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Tuberculosis in the Tintswalo district of the Northern Province

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TUBERCULOSIS IN THE TINTSWALO DISTRICT OF THE NORTHERN PROVINCE

A study of:

* patient admissions 1992-1995
* decentralisation and integration of services within district clinics
* treatment outcomes and their influences
* patient perceptions, behaviours and experiences

Mary E Edginton

A dissertation submitted to the Faculty of Health Sciences, University of the Witwatersrand, in fulfilment of the requirements for the degree of Doctor of Philosophy

Johannesburg 1998

DECLARATION

I declare that this thesis is my own work. It is being submitted for the degree of Doctor of Philosophy in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Signed: ..... Date 30th June 1998

DEDICATION

This work is dedicated to all patients suffering from tuberculosis, especially those in the Tintswalo district, with the hope that they will by cured through excellent health services









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This work could not have been done without a very special person - my dear husband, John. In so many ways, he provided the time and space for me to work, and was always there to encourage and support.

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I acknowledge the contributions of my supervisor, William Pick, and thank him for his thoughtful comments and his help, and for countenancing periods of absence from the urban base of the department.

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ABSTRACT

This study is divided into two phases, an historical record review and an intervention study. In the period 1992 to mid-1994, tuberculosis management and treatment outcomes were reviewed in the Tintswalo district of the Northern province, South Africa. Bacteriological coverage, diagnostic criteria and treatment outcomes for the 514 patients in this period were less than the internationally recommended goals, a record review giving a best estimate of treatment completion of 67% for new smear positive patients.

An intervention study was set up from mid 1994 until January 1996. Twelve district clinics were randomised to either "treatment" or "control", depending on whether tuberculosis follow-up was at the hospital or clinics. Treatment clinic staff were trained, treatment supporters were organised, and the logistic needs of a good tuberculosis control programme (transport to the laboratory and drugs supplies) were provided by the researchers, who collected data on patients, disease management and outcomes. A higher proportion of patients were diagnosed bacteriologically, the majority had supporters, and treatment outcomes for all new smear positive patients who lived in the district improved significantly to 81%. There was no change in outcomes for those living outside the boundaries of the study district. Successful treatment outcomes were more likely in supported patients, in new, as opposed to re-treatment patients, and in those with at least a minimum level of formal education. Patients were interviewed at different stages of their treatment. The results, together with those of focus group interviews on patients and other community members, provided insights into the problems experienced by patients, and their preferences, and into local beliefs and attitudes about this disease. It was concluded that good tuberculosis management in this rural district was possible, despite a number of constraints. It required commitment, staff training and support, management supervision, and organisation of a laboratory network and drug supplies.

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PREFACE

This thesis focuses on the management of rural district health services whose aim was the successful treatment of tuberculosis. Management includes processes of planning, organisation, leading and controlling which, if well practised, will result in an organisational structure in which trained, motivated and supervised staff, adequate and appropriate resources, and systems for monitoring and evaluating processes and outcomes, will ensure the best possible treatment outcomes with patient satisfaction.

The policies of the leading international organisations concerned with tuberculosis control, the World Health Organisation and the International Union against Tuberculosis and Lung Disease, states that for control programmes to be effective, there must be government commitment to and policy on tuberculosis control, recommended means of detecting cases, standardised treatment regimens targeted at the defined priority patients, adequate drug supplies, and a standardised recording system for evaluation.

The elements of this policy package cannot be provided, nor successfully implemented, in the absence of good district health management, the district being the level at which basic health care provision is implemented.

The work of this thesis includes the description of how tuberculosis was managed in a rural district of the Northern Province in South Africa during the early 1990s, and with what results, a description of the process of intervention set up by the researcher to decentralise management to some district clinics, and the results of that intervention process.

An integral part of the study was a series of interviews with patients to measure their

perceptions, beliefs and behaviours. Finally there is a discussion on the implications of the decentralisation process for this and other rural districts in South Africa. Recommendations are made that may be relevant to other districts in South Africa.

The section on the research process is preceded by a literature review on tuberculosis. This review attempts to summarise much of the known, researched facts about many facets of this disease, in order to provide background material on the complexity of the subject. Tuberculosis is not a health problem for which there are easy solutions. There is a need for some understanding of the history of the disease, and its pathogenesis with known and unknown facts about the host-environment-organism interaction, because such knowledge can contribute to new methods of diagnosis and treatment. Recommendations about diagnosis and treatment of tuberculosis, based on international research, provide a basis for considering how and where programmes should be implemented, and how to interpret and use experiences of successes and constraints from other countries. Critical to the successful treatment of this disease is patient adherence, a complex phenomenon dependent on a number of factors. Studies and reviews on adherence are presented. The South African situation regarding tuberculosis is described, with reports of programmes in different parts.
The final section of the literature review describes the district health system as proposed and implemented elsewhere, and as it is evolving in South Africa. This is necessary to contextualise the system within which tuberculosis control programmes should operate to be effective.

Little justification is needed to research tuberculosis, a disease proclaimed a global emergency by the World Health Organisation in 1993. The quotation below summarises its priority status.

The combination of the enormous burden of the disease, years of neglect, the existence of effective interventions, and the availability of one of the most cost-effective interventions must make tuberculosis one of the highest priorities for action and research in international health

Murray C, Styblo K, Rouillon A. Tuberculosis. In: Disease Control Priorities in Developing Countries. editors Jamison DT, Mosley WH, Measham AR, Bobadilla JL. New York: Oxford University Press, 1993.

SECTION 1

LITERATURE REVIEW

The aim of this section is to review the basic concepts of tuberculosis in order to provide a background for the study to be described in subsequent sections. This section has the following chapters:

1. The history of tuberculosis
2. Pathogenesis and risk factors
3. The measurement of the global tuberculosis problem
4. Diagnosis and case finding
5. Prevention
6. Chemotherapy
7. Tuberculosis control programmes
8. Treatment adherence
9. Tuberculosis in South Africa
10. The district health system and the integration of tuberculosis services

CHAPTER 1

THE HISTORY OF TUBERCULOSIS

This chapter includes:

Early history

The discovery of the causative organism

Treatment before chemotherapy

The present era of chemotherapy

1.1 Early history

There is evidence of tuberculosis in humans since early civilisation. Spinal disease has been identified in Egyptian mummies dating from 4 000 BC,[1] from several skeletons of neolithic times between 5 000 and 4 000 BC,[2] and from Britain at the time of the Roman occupation.[3]

More detailed descriptions of the disease and the rates of infection are available from around the 17th century, when 20% of deaths in London and other European cities were attributable to tuberculosis.[4] It swept across Europe earning its name "the White Plague" and was also to be found in America and Asia. By the early 1800s, an estimated 50 million people in London and New York had infectious tuberculosis with 7 million TB deaths occurring annually.

At this time theories about the cause of TB ranged from "contagion" or evil spirit-induced, to air-borne transmission (first propounded by Aristotle).[5] Treatment consisted of "hygienic measures" with personal protection against cold and exercise in the open air, and "collapse" treatment in which air was introduced into the pleural cavity to rest the affected lung.[6]

1.2 The discovery of the causative organism

In 1882 Robert Koch, a German microbiologist gave the world the information needed to study the disease further, and to find a cure. He used a blue dye stain to identify organisms in tissues of people who had died from tuberculosis, reinjected these into laboratory animals, isolated the microscopic "rods" from the animals, grew them in culture media, and finally caused disease in animals by injecting as well as spraying animals with cultured bacilli.[7] His research was a landmark in the long saga of attempts to eradicate this disease. The identification, reinfection of animals, and re-isolation are the basis of Koch's postulates for causation, of relevance today for communicable diseases.

1.3 Treatment before drug therapy

The "acid fast mystery" was not to be solved easily and the development of effective anti-tuberculous drugs was to take another 60 years, until streptomycin became available in 1944, to be followed by para-amino salicylic acid in 1946 and isoniazid in 1954. Until these drugs were discovered and made available, TB sufferers were sent to sanatoria in warmer parts of Europe, America and later elsewhere in the world. In the sanatoria era of 50 years ago patients and their treating doctors were isolated in institutions for one, two or more years.[8]

1.4 The present era of chemotherapy

Tuberculosis remains one of the world's major health problems, despite the fact that it has been known for millennia, that effective treatment is available, and that recently developed technology is enabling studies at molecular level. The goal of eradication still seems as far off as it must have done in 1882.[6] Multiple drug resistance and HIV-associated disease

have brought the tuberculosis situation into a new era. We are being forced to reconsider historical concepts of heredity, contagion and environment, and to focus efforts on primary prevention of spread.[9] Molecular epidemiological and genetic research efforts are currently being directed to addressing the gaps in our knowledge regarding *M.tuberculosis* virulence and host defence.[10] Successes will be marked by the development of new drugs, a vaccine and other immunological interventions.

However eradication of tuberculosis depends not only on further knowledge about the causative agent, and on therapeutic advances, but on favourable political systems, addressing the fact that profits are not available to pharmaceutical companies researching new drugs and improving national health infrastructures.[11]

CHAPTER 2

THE PATHOGENESIS OF AND RISK FACTORS FOR TUBERCULOSIS

This chapter includes:

The etiological agent

Exposure and infection

Progression from infection to disease and risk factors

The natural history of the disease.

2.1 Etiological agent

Tuberculosis is caused by the bacillus *Mycobacterium tuberculosis,* an organism which replicates slowly and spreads mainly by airborne transmission from persons with active disease. When bacilli can be microscopically identified in sputa specimens, such disease is termed smear positive. It is the stage of pulmonary tuberculosis which is most infectious. Organisms are capable of invading and killing host cells, of remaining dormant for periods, and of eliciting immune responses that cause the tissue damage associated with the disease. The chain of events in the pathogenesis of tuberculosis disease involves exposure to the organism which may cause infection, which may proceed to disease.

2.2 Exposure and Infection

Infection is a prerequisite for disease and is dependent on exposure to individuals with infectious tuberculosis. Organisms enter a host body and stimulate a beneficial cell-mediated immune response, as well as a delayed hypersensitivity reaction which is responsible for the tissue damage caused by caseation and cavitation, and for the skin reaction in infected individuals.[12] Infection is measured by reaction to standard skin testing (tuberculin tests). There appears to be no threshold of organisms required to produce infection.[13] Various

factors operate in association with the causative organisms and can be classified according to their roles in pathogenesis.[14] Factors involved in exposure and infection are essentially extrinsic to individuals exposed, whereas risk factors for the progression of disease are endogenous and part of the characteristics of the individual.[15]

2.2.1 Extrinsic factors:

The risk of exposure to tubercle bacilli depends on the number of infectious cases in a community, the length of time they have been infectious and the interactions between infectious cases and contacts. Close contact with infectious (smear positive) persons in the same household has been shown to be the greatest risk.[16] A recent study in a high prevalence region of South Africa confirmed this risk, with 34% of children under the age of 5 years, living in the same households as index cases, developing disease.[17]

Casual contact can result in infection under certain circumstances, as described in a recent account of infection occurring in a number of people who had had contact with an active case during several consecutive airplane flights.[18]

2.2.2 Annual risk of infection:

This is the probability of an individual becoming infected with tuberculosis in the course of one year. Infection prevalence expressed over time provides a useful tool for measuring the risk of tuberculosis.[19] The annual risk of infection as studied in different age cohorts of populations reflects the rate of transmission of disease. In developed countries of the world, active disease is now less common and the rate of infection is higher in older persons (80% over 50 years), reflecting active transmission years ago. In such populations, an increasing proportion of cases is likely to occur in the elderly due to reactivation. In developing countries the annual risk of infection is high, ranging from 0.5 to 2.5%, with the majority (77%) of

infected individuals below 50 years of age. In these populations the majority of cases will be attributable to recent primary infections or reinfections.[20,21]

In the majority of cases, primary tuberculous infection is isolated by the granulomatous reaction of the host, and causes a subclinical response.

2.3 Progression from infection to disease and the intrinsic risk factors

2.3.1 Molecular biological and genetic factors:

Understanding the pathogenesis of disease and the determinants of failure of the immune response of certain individuals is the aim of current molecular level research. It has been known for some time that virulence factors released by Mycobacteria prevent macrophages from destroying phagocytosed organisms.[22] New work demonstrates that there may be a gene-controlled host macrophage ability to resist mycobacterial invasion, and that deficiencies in the cell-mediated response contribute to active disease.[23]

The clone library of *Mycobacterium tuberculosis* chromosomes is currently being constructed. The precise function of about one third of genes is known. A process of replacement of genes with inactivated versions will provide knowledge about particular characteristics of the organisms such as virulence and dormancy, and will hopefully be the path to new drug and vaccine development.[24]

Ten percent of infected individuals with normal immunity will develop tuberculosis disease within their lifetime.[25]

2.3.2 Reactivation or reinfection:

In developing countries with high annual risks of infection, active transmission of organisms is responsible for infection and reinfection. In developed countries with low annual risks of

infection and low rates of smear positive disease, the disease would seem to be reactivation of previous primary disease. Risk factors operate to facilitate that process.

The assumption that most tuberculosis disease in older people is the result of reactivation of previous infection is being challenged now that the new molecular epidemiological technique, DNA fingerprinting by restriction-fragment-length polymorphism (RFLP), is available and providing evidence that much current tuberculosis is due to active transmission.[26] Clustering, indicating recent infection, accounted for one third of a series of cases in San Francisco, and nearly two thirds of those human immuno-deficiency virus- (HIV-) infected.[27] Further application of this technique for investigating transmission in communities will provide definitive answers.

The implication for programmes that reinfection may be significant is that transmission is only halted by curing the infectious cases. The appropriate intervention for reactivation is chemoprophylaxis for those who have risk factors.

It is estimated from surveys of incident and prevalent infectious disease that an undiagnosed, untreated smear positive case infects between 10 and 14 persons per year.[25] Between 6% and 8% of those primarily infected will develop disease.[28] Thus each infectious case can result in 0.6 to 1.2 cases of tuberculosis disease within a mean period of 1.4 years. Cases will be equally distributed between smear positive and other forms of tuberculosis.

2.3.3 Risks for infection progressing to disease:

A number of "endogenous" host related factors have been shown to be risks for the development of tuberculosis disease.

i) Young age and recent infection

Young children have immature immune systems which cannot contain infection. In

developing countries where the risk of infection is greater in younger ages of the population, transmission of disease is high. Infection within the previous seven years, especially in the previous year, has been shown to be a risk for development of disease. Half the 10% lifetime risk occurs in the first 5 years of life.[29]

ii) HIV

Infection with HIV has been shown to be the strongest factor known for progression of tuberculous infection to disease. Tuberculosis in high prevalence countries is an opportunistic disease of HIV.[15, 30, 31, 32]

Evidence of the problem was first noted in 1985 when cities experiencing the new Acquired Immuno-Deficiency Syndrome (AIDS) epidemic also had the highest incidence of tuberculosis.[33] In New York, during nine months of 1988, 224 cases of tuberculosis were admitted to a hospital. Risk factors as measured by multivariate logistic regression were HIV/AIDS, homelessness, and alcoholism. [A high proportion of patients (89%) was lost to follow-up.[34]]

This was the beginning of awareness of the potential impact of HIV, but other social factors were clearly important in the resurgence of the disease in the United States which correlated with withdrawal of government funds and the "total failure of a public health system" - the U-shaped curve of concern.[35]

Human immuno-deficiency virus destroys the cellular immune system (T cells or macrophage function, or both) necessary to prevent the progression of tuberculosis infection to disease. The initial mechanism for development of tuberculosis in HIV- infected persons is thought to be reactivation of infection. In countries with a high prevalence of tuberculosis infection, significant increases in active tuberculosis in HIV-infected persons will result as they become

immuno-compromised. With more active disease in communities, there is more likelihood of spread to HIV-negative individuals.[36] New evidence is now available that shows that HIV-infected individuals can develop rapidly progressive disease from recently acquired infection.[37,38]

The annual risk of breakdown to disease in persons co-infected with tuberculosis and HIV is 5% to 15%.[39]

The seriousness of the situation prompted an experienced tuberculosis expert to ask "if it is still useful to speak of elimination in developed countries and of an efficient control programme in developing countries when HIV has been constantly increasing in the whole world?".[40]

Global trends attributed to tuberculosis-HIV co-infection:

In 1990 it was estimated that over 1700 million people worldwide were infected with *M. tuberculosis*. About ten percent (170 million) lived in Africa where the high prevalence of HIV infection (up to 25% in some reports), was already causing a major increase in the incidence rate.[41] In Asia and the West Pacific where over 1000 million people live, there were about 5 million of the world's 8 million cases of tuberculosis, and the highest proportion of the world's tuberculosis infected people. Even a low prevalence rate of HIV infection would cause a dramatic increase in the disease. By 1994 there were, in fact, reports of increasing numbers of HIV-infected persons in Asia.[39,42]

By mid-1994, the WHO estimated that globally over 16 million adults and over 1 million children were infected with HIV, 90% of these in the developing world and mostly in people 15-49 years of age. The impact of the co-infection will be greatest in countries where

there is a high proportion of people in this age group. Of the estimated 5.6 million co-infected people in the world, most, 3.8 million, live in Sub-Saharan Africa and 1.2 million in Southeast Asia. Tuberculosis incidence rates in several African countries have been rising since the late 1980s, despite better or unchanged control programmes, as a result of HIV-infection.[43] Mathematical modelling was used to predict that, at the expected rates of risk of tuberculosis and HIV-infection in Africa, by the year 2000, there will be massive (4 to 10-fold) increases in smear positive tuberculosis rates between 1980 and 2000.[44] Another paper has predicted a doubling of incident cases in sub-Saharan Africa between 1990 and 2000, with 50% of the increase attributable to HIV.[45] In 1996, global estimates of the number of HIV-infected people were close on 30 million, 63% of whom (14 million people), were in Sub-Saharan Africa.[46]

A review of programme reports showed that tuberculosis case rates since 1985 rose twice as fast in countries with high HIV seroprevalence. However, stratification by quality of tuberculosis control demonstrated a decrease in the rate of rise with better control programmes.[47]

iii) Poverty

Poverty has long been associated with tuberculosis. Socio-economic improvement with better living conditions was associated with the decrease in the mortality rate in England during the pre-chemotherapeutic era. The recent upsurge in various parts of the world is thought to be partly attributable to poverty, homelessness and general social deprivation.[34] A recent analysis from England confirms that poverty may be a factor in the recent increase of the disease, as reflected by findings of significant correlations between tuberculosis and various indices of poverty.[48]

iv) Silicosis

A relative risk of tuberculosis of 30 has been reported for individuals with silicosis, compared with those without.[49] The mechanism appears to be an impairment of macrophages by silica dust. A cohort study followed gold miners in South Africa over seven years, 818 with silicosis and 335 without, and found a relative risk for tuberculosis of 2.8. The conclusion was that 25% of men with silicosis would develop the disease by the age of 60 years.[50]

v) Smoking

Cigarette smoking has been shown to be a risk factor for the development of tuberculosis. A study in China showed a relative risk of 2.2 for heavy smokers (defined as 400 or more cigarettes per year) compared with non-smokers, when adjusted for age, work, sex, history of contact and area of housing.[51] A more recent case control study from the United States found that patients had almost twice the risk of having tuberculosis if they had smoked for 20 years or more, when adjusted for age and alcohol consumption.[52] Young adults studied in Spain were found more likely to have tuberculosis if they smoked, with an odds ratio of 5 for those who were both active and passive smokers. This case control study showed a dose-response relationship with the number of cigarettes smoked daily.[53]

vi) Alcohol

Buskin et al showed that those with heavy alcohol consumption had twice the risk of developing tuberculosis compared with those who did not drink, when adjusted for both age and smoking.[52]

vii) Older age

Older age has been shown to be a risk for tuberculosis.[54] A recent incidence study of clinic attenders in the United States showed a threefold risk of patients 70 years or more, compared

with young adults.[52] The higher incidence in older persons in developed countries is probably related to reactivation of primary infection. Once pulmonary tuberculosis develops in an older person, the disease does not show any specific pattern. [55]

viii) Lung fibrosis

Fibrotic lesions of the lung from untreated tuberculosis are a risk for the development of disease.[56]

ix) Other risks

Other reported risks are a number of medical conditions including underweight, diabetes, immuno-suppressive therapy, certain cancers, haemophilia, and gastric and small intestinal removal or bypass surgery.[57]

2.3.4 Relationship between risk of infection and risk of disease.

An empirical relationship between risk of infection and risk of disease has been established based on a constant relationship observed in data available from different communities. For developing countries, it was found that a 1% risk of infection corresponds to an incidence of 50-60 cases of smear positive tuberculosis per 100 000 population.[58] The relationship was confirmed from other developing country data with a calculated figure of 49 smear positive cases per 100 000 population per 1% annual risk of infection. For developing countries with an annual risk of infection of 1-2%, it is calculated that 1.22 cases of smear negative and extrapulmonary disease exist for every one case of smear positive tuberculosis.[28]

2.4 Natural history of disease

Without treatment, 50% of cases would die within 5 years, 30% would recover and 20% would remain sputum positive (and remain a risk to the community in which they live).[59]

CHAPTER 3

THE MEASUREMENT OF THE GLOBAL TUBERCULOSIS PROBLEM

This chapter will describe:

Trends over the last 100 years

The situation since 1974

Reasons for the increase in disease

3.1 Trends over the last 100 years

The severity of tuberculosis is measured from incidence of disease, usually calculated from notifications of new cases, annual risk of infection, and mortality rates. Incidence and mortality have been measured and documented in developed countries since the mid 1800s. Mortality rates in England, Europe and North America were decreasing from 1850 before the discovery of the causative organism, with a steep downward trend after 1910. This was undoubtedly due to improvement in socio-economic conditions, but also to the fact that infectious cases were isolated in sanatoria and not spreading disease.[60] The decline continued despite world wars and the economic recession of the 1920s and 1930s. The impact of chemotherapy was dramatically demonstrated by a population intervention study performed among the Eskimos between 1950 and 1970. Until early 1950, rates of

1 500 to 2 000 cases per 10 0000 population were recorded every year. A tuberculosis control programme using drug treatment was introduced during the 1950s and resulted in an annual decline in the risk of infection to a level in 1970 (20 years later) equivalent to that achieved in 100 years in the pre-chemo-therapeutic era.[61]

3.2 The situation since 1974

By the 1980s, many developed countries reported incidence rates of below 30 per 100 000. For developing countries, the situation has been different. Reliable data has not been available. The rates are unlikely to have improved, in fact with unchanged socio-economic conditions, population growth and increasing poverty, they may have worsened as the disease was introduced and spread by settlers. Data from these countries remain incomplete, resources for diagnosis and health services being scarcer than in industrialised countries. The estimates quoted below have been made based on extrapolations for countries where data is incomplete, and on epidemiological models developed from observations of incidence of smear positive disease rates for differing annual risks of infection.[20]

3.2.1 Prevalence or annual risk of infection:

Tuberculosis prevalence, as measured from annual risks of infection with extrapolation for age distributions and trends of previous infection risks, was calculated for world regions in 1990. Based on these it is estimated that one third of the total world population is infected. In Europe and North America the annual risk of infection with *M. tuberculosis* has been falling for many years, and infection is limited to elderly people and high risk groups - the homeless, alcohol and drug users, and immigrants. Annual incidence has fallen to around 10/100 000. In developing countries the annual risk of infection is high (1-2% per year). The disease has never been controlled, incidence rates being over 200/100 000 even before the HIV era.[62]

3.2.2 Incidence of disease:

Direct measures of disease incidence are dependent on notifications. Annually 2.5 million cases were reported during the period 1974 to 1983, with a rate of 70 per 100 000 in Africa compared with 9 per 100 000 in the United States. Over the period there was an increase in

numbers of cases and in rates in Africa and South East Asia, and a decrease in rates everywhere else.

Using the annual risk of infection estimates, and the formula of 49 smear positive cases per 100 000 population per 1% risk and 1.22 non-smear positive cases per smear positive,[28] estimates of incident cases were calculated.[45] About half the cases expected globally, and one quarter of those expected in Africa, had been reported. The global number of cases for 1990 could be 8 million, with 1.2 million in Africa.

Another method of estimating incidence was based on selected regional sentinel reporting sites which were extrapolated to whole countries. These could well be underestimates since the best reports are incomplete in many regions. New case estimates for 1990 were 7.5 million, with 3 million in South East Asia, 2% of whom were attributable to HIV, and 1 million in Africa, 20% of whom were attributable to HIV.

Projections for 1995 and 2000 are that there will be a 16% and 36% increase respectively. By 2000 the incidence in Africa will have doubled to 2 million per year, 29% of cases attributable to HIV.

3.2.3 Smear positive disease:

Based on the incidence of smear positive cases in Tanzania, the smear positive incidence rate worldwide was 77 per 100 000 with 103 per 100 000 in Africa. Eighty percent of all smear positive tuberculosis occurs in adults between the ages of 15 and 54 years.[28]

3.2.4 Mortality:

Deaths are under-reported in developing countries. Therefore mortality rates for 1990 have been projected assuming that 50% of untreated cases died and that notified cases died at a rate of 15%, only about half being cured. Further refinement in the calculation must be for the

proportion of cases who received treatment, with a lowering of the 50% case fatality to a mean of 45% for Africa.[28]

The estimated annual death rate was highest for Africa (100 deaths per 100 000 population), and under four per 100 000 for Europe. For Africa, only 2% of the expected deaths were reported between 1988 and 1990.

In 1990, an additional 150 000 deaths were attributed to HIV- associated tuberculosis, most (82%) occurring in Africa.[20]

Almost 90 million new tuberculosis cases and 30 million TB deaths are expected in the decade before 2000 at the present levels of intervention. Ninety five percent of the new cases will be in developing countries.[45]

3.3 Reasons for increase in disease incidence

The reasons for the current tuberculosis epidemic in the world have been highlighted by the WHO.[63]

i) **Poor control programmes** that prevent deaths, but keep infectious tuberculosis individuals alive to act as transmission sources. (Tuberculosis control programmes will be described in chapter 7.)

ii) **Demographic trends**

With increasing population growth in recent years, there are more people who were infected as children, and who are now in the ages at greatest risk for tuberculosis disease.

iii) **HIV infection**

The most dramatic impact on global incidence of tuberculosis has already been made, and will

continue to be made by HIV infection.

iv) Social and economic trends

Economic and political shifts, wars, famines and natural disasters have worsened the state of poverty in many developing countries, and have weakened health services. Migration and refugee movements are greater than at any time in history, resulting in much more potential contact with infectious people. Widescale urbanisation, without adequate resources for appropriate living conditions, and with health services unable to cope with health needs, has provided the conditions for the development and spread of tuberculosis.

v) The emergence of multi-drug resistance

Poor programme and poor treatment practices have created resistant strains of *Mycobacterium tuberculosis*. Acquired resistant disease can spread directly to contacts as primary resistant disease. This problem is associated with high mortality and very high costs for which treatment is not 100% effective.

CHAPTER 4.

DIAGNOSIS AND CASE FINDING

The chapters on diagnosis and treatment focus on pulmonary tuberculosis, the transmittable form of the disease. Extrapulmonary disease is diagnosed according to the site of involvement, and often requires specialist advice and techniques which are outside the immediate scope of a tuberculosis control programme.

This chapter includes:

- *Clinical features of tuberculosis*
- *Bacteriological tests*
  - *microscopic*
  - *culture*
- *Chest radiography*
- *Tuberculin skin tests*
- *Other newer tests*
- *Issues in diagnosing HIV-infected patients*
- *Case finding (identification of patients with disease, and implementation of tests within programmes)*

4.1 Clinical features

Suspicion that a patient may have tuberculosis is based on the presence of clinical signs and symptoms. Those suggestive of pulmonary tuberculosis are a cough for more than 3 weeks, weight loss and sputum production. Other respiratory and systemic symptoms and signs include haemoptysis, dyspnoea, chest pain, fever, night sweats and anorexia. A review showed that, at the time of diagnosis of disease, 84% of patients had been coughing for less than 6 months, 60% for less than 3 months. Cough and haemoptysis were said

to be the most "discriminatory" symptoms.[64]

It would be entirely impractical and unfeasible to do bacteriological tests on all patients presenting to a health service, or all those with respiratory symptoms, even in areas of high tuberculosis prevalence. The predictive value of the microscopy test in such situations of low positive specimen prevalence would be very low. Patients should be screened to identify those with clinically suspicious disease, thus increasing the prevalence of disease in those investigated further, and raising the positive predictive value of the microscopy test.[65, 66]

4.2 Bacteriological tests

The diagnosis of pulmonary tuberculosis is confirmed with the identification of the organism *Mycobacterium tuberculosis* in sputa of individuals.

4.2.1 Microscopy:

Microscopy is the method of diagnosis recommended for national control programmes as it is relatively simple and able to detect those cases of disease which are infectious, thus of public health importance, as well as representing advanced disease requiring treatment for the individual. Examination of the sputum should be used as a primary case finding method without the additional use of X-rays.[67, 68, 69]

Sensitivity of microscopy: The chances of finding organisms in a microscopy specimen increase with the concentration of bacilli in the specimen, the number of specimens examined, and with the skill of the microscopist. Specimens containing 6 000 organisms per millilitre have a 50% probability of being read as positive. When the concentration of organisms

increases to 100 000, positive results will be recorded more consistently, that is the sensitivity increases.[70] Several studies have confirmed the range of bacilli per millilitre for detection to be between 5 000 and 10 000.[64] A good laboratory has overall sensitivity results for microscopy using the conventional Ziehl-Neelson stain of about 60%. Rates reported from several African laboratories range from as low as 9% to 46%.[71] The reported rates in the United States vary between 50% to 81%, depending on clinical presentations as well as laboratory factors.[72]

In Tanzania, a sensitivity of the smear test was 93% in field conditions measured against nearly 5000 culture positive cases. In order to measure the efficiency of the smear detection rate in Tanzania, a comparison was made between smear results and figures for the expected incidence rate of disease based on the annual risk of infection and notification rates. Smear tests had picked up 79% of expected cases, demonstrating their robustness and efficiency in field conditions.[68]

In HIV-associated tuberculosis, the sensitivity rate was found to be lower (63%) than in HIV seronegative patients (82%) in a study in Zambia.[73] The range in other studies was 31% to 82%.[74] The sensitivity of the smear test depends on the stage of HIV-infection, being similar to that in non-HIV-infected patients in earlier stages.

Specificityof microscopy is higher than sensitivity, generally 99% or more.[72] There are a few situations that may cause false positive results, including non-tuberculous Mycobacteria. However these do not account for significant disease in HIV-infected patients.[62]

The **fluorescent microscopy technique,** which uses an auramine stain, increases sensitivity

slightly and is faster and easier to perform, thus useful for laboratories examining large numbers of specimens. This technique ultimately lowers costs because a microscopist can examine 30-40 specimens in a day using the conventional Ziehl-Neelson stained slides, but 200 or more with the fluorescent technique.[75]

In a patient with disease, two specimens of sputa will read positive in between 85% and 95% of smear tests. Adding further specimens will not increase the yield significantly.[76,77] Although more specimens would detect the remaining 5-15%, the difficulties for patients returning with specimens, and the potential overloading of laboratories make the collection and examination of two specimens the most practical solution, certainly in developing countries. When programmes are more advanced, it would be better to test 3 specimens per suspect.

An overnight (early morning) specimen is better than a spot specimen, according to a review of a number of studies.[77] The two specimens should thus ideally be one spot and one next day.

Issues relating to specimen collection and examination:

A number of organisational and quality issues are crucial to the success of microscopy for diagnosis. These include correct and safe collection of specimens, appropriate storage to reduce bacterial overgrowth, transportation to a district laboratory as soon as possible, quality control at the laboratory, and rapid reporting of results to the relevant health facility. Standards for laboratory reporting of smear results are in general use, expressing the number of bacilli per microscopic field.

Patients with active disease should be diagnosed and treated as soon as possible to prevent further morbidity and possible mortality, and to prevent spread of disease. A study from an academic hospital in Malawi has reported delays for smear positive in-patients between diagnosis of tuberculosis and the onset of treatment. Almost 70% did not start their treatment until 5 days after admission, 11% took more than 16 days. Infectious patients are a danger to ward staff who are HIV-infected, and thus at great risk.[78]

Organising laboratory services:

Within tuberculosis control programmes, it is essential to consider the organisational needs of the diagnostic services. The use of three types of laboratories has been proposed - central or specialised, usually located in a city, intermediate with tuberculosis services within a large laboratory, and peripheral laboratories in clinics.[79] The advantages of a network of microscopy services at district level are the accessibility and theoretical ease of performing on-site tests for patients at the time of their clinic visits. However disadvantages include the need for equipment and supplies, for microscope maintenance, for training and supervision and quality control of microscopists, and for safe management of specimens and material. Aluoch et al, reporting on studies in Kenya, demonstrated that patients with clinical features suggestive of tuberculosis had not been investigated, and had been missed by health services staff, despite several clinic presentations by the patients. They concluded that case finding would be more effective if concentrated at district hospital level.[80] Others have agreed with the need for a degree of centralisation, although solutions have to be found for differing local situations.[79]

4.2.2 Culture tests:

Culture positivity is regarded as the gold standard in diagnosing tuberculosis. Culture examination requires a good laboratory, is usually only available at central levels, is more expensive, and takes time for the organisms to grow. On conventional Lowenstein-Jensen media the mean time is 6 weeks. The radiometric BACTEC results are usually ready within 2 weeks. Culture testing increases the number of new cases found by up to 30%, and is able to differentiate non-tuberculous Mycobacteria.[69,70] Reported sensitivity is over 80%, with up to 98% in cavitatory disease. Specificity is almost 100%.[72] For programme conditions, the question that has to be asked is whether smear examination is adequate for diagnosis or whether routine culture tests should be added.

There are two situations for consideration. The first is the **smear positives**. It has been shown that culture confirmation of two positive smear results is not necessary, since culture tests confirmed smear results in all but 4% of those tested. Persons with clinical features suspicious of disease and smear positive results, but who do not have culture confirmation, are in little danger of over-treatment.[81]

The second situation is the **smear negative** cases in view of the fact that smear negative, culture positive cases occur. Such cases are in an earlier stage of disease and do not present a public health problem. However smear negative cases with active disease may develop serious disease. If smear negative tuberculosis is not diagnosed, health services will only be identifying late stage disease for treatment.[79]

For patients whose clinical and radiographic features are suspicious of disease, but in whom smears are negative, an option is to perform culture tests and commence empiric

therapy while awaiting culture results. One study showed that half such smear negative cases had disease - 12% had positive cultures and 36% were diagnosed on response to therapy. The remaining half were treated for disease that was not present.[82] It is generally agreed that a definitive diagnosis must be made. The prognosis of smear negative lesions that are positive only by culture has been proved to be better than previously thought since spontaneous healing occurs.[76] Under operational conditions positive smears have been found in 50%-70% of patients who subsequently have a positive culture. Two smears together have about the same rate of positivity as a single culture.[83]

The active search for patients who are smear negative, but may be culture positive has a low priority in tuberculosis control. Programme emphasis must be on the smear positive patients.(83) Further evidence of the lower public health importance of smear negative, culture positive cases comes from an earlier study in which it was shown that the smear positive patients "caused" infection in 65% of child contacts compared with 29% who had been exposed to smear negative, culture positive patients, and 18% who had contact with smear negative, culture negative cases (and 22% in controls with no contacts).[84]

Culture has a place in programmes for patients suspected of being resistant, as drug susceptibility tests require cultured organisms.

The penalties of over-diagnosis are that the patient is exposed to unnecessary drugs and possible side or toxic effects, and to social stigmatisation with possible loss of a job, while the health service wastes valuable resources, diverting these from infectious cases. Standards and practices for diagnosis are thus crucial.[85]

Bacteriological diagnosis in summary:

The WHO-organised meeting of international consultants late in 1990 declared that the sputum smear test effectively identifies individuals who are most infectious, is cheap, simple and easily implemented at peripheral levels. It also provides a way to evaluate programmes by measuring conversion to smear negative after appropriate treatment. A weakness is the low sensitivity of microscopy so that not all culture positive cases are detected. Culture testing could improve the detection of cases, but is expensive, difficult to perform, requires sophisticated equipment, and takes some weeks for results to be available. Culture examination should not have routine application in control programmes in developing countries. When bacteriological confirmation of tuberculosis is below 70%, it indicates that there is under-utilisation of bacteriology or over-emphasis on radiography.[86]

4.3 Radiological diagnosis

Chest X-rays, when available, have a role in the diagnosis of patients who have symptoms and signs suggestive of the disease. Screening of patients by identifying those with symptoms and radiological features can reduce the number of sputum examinations required.[86] However X-rays have been relied on excessively.[68] There are many examples of missed radiological tuberculosis lesions (under-diagnosis),[87] while other diseases of the lungs may be mistaken for tuberculosis (over-diagnosis). Only bacteriology can provide the final proof.[88]

Mass radiography:

Mass radiographic examination fails to detect all the new sources of infection in a

community, and is unable to diagnose smear positive disease before patients present with symptoms.[63, 89] For these reasons, and those of poor availability and high costs in most countries, the WHO expert Committee recommended that indiscriminate case finding by mass radiography be abandoned.[90]

4.4 Tuberculin skin tests

Tuberculin skin tests have a very limited role in case finding, especially in countries with a high annual rate of infection and where BCG vaccination is used. The sensitivity and specificity are low.[86, 91] Tuberculin tests have a role in the diagnosis of children with tuberculosis.[92]

4.5 Other newer tests

In the quest for more efficient means of diagnosing tuberculosis, a number of new approaches have been explored.[93] One aims at measuring host response. Enzyme-linked immunosorbent assays (ELISA) have been developed, and while they appear to be highly sensitive, they have not yet found application in field conditions, where identification of smear positive disease remains the priority. For pleural tuberculosis, raised enzyme levels of adenosine-deaminase have proved to be useful. The other main direction of development has been in detecting bacillary constituents by measuring antigens, structural lipids, and more recently, DNA probes using polymerase chain reactions (PCR). This test is very sensitive but false positives result from contaminants. Neither the ELISA nor the PCR tests appear to add to the diagnostic yield when sputum smears are available. PCR may have a useful application in the diagnosis of pleural and extrapulmonary tuberculosis.[72]

4.6 Issues around the diagnosis of HIV-related tuberculosis

The era of HIV has complicated the diagnosis of tuberculosis. Many studies have shown that there is a higher rate of extrapulmonary disease as the degree of immuno-suppression increases. With less advanced HIV infection, extrapulmonary disease occurs in 24-45% of patients, while with more advanced HIV infection, this increases to over 70%.[74] In the earlier stages of HIV infection where immuno-suppression is less, the sensitivity of sputum smears is similar to that of HIV negative individuals. With progression of HIV-caused immunosuppression, the smear sensitivity decreases. This is because the classical cavitating disease with excretion of bacilli is less common as extrapulmonary and atypical disease becomes more common. Specificity is also reduced, possibly because non-tuberculous Mycobacteria are more frequent, although this has been disputed. Overall, HIV-positive patients are more likely than HIV negatives to have sputum negative or extrapulmonary tuberculosis, and in those with pulmonary disease the radiological manifestations are more likely to be atypical.[62, 74, 94, 95]

Radiographic changes in the less immunocompromised stages show the classic upper lobe, cavitating, fibrotic disease pattern, while later the pattern is one of lower lobe infiltrates, hilar adenopathy or even a normal X-ray pattern.[62, 74]

In a study of 289 Haitians in 1988, 215 of whom were HIV- seronegative and 74 seropositive, the difference in sensitivity of smears (79% and 66% smear positive for HIV negative and positive individuals respectively) was regarded as insufficient to "compromise the diagnostic utility of the sputum smear".[96] It should be noted that this period was relatively early in the HIV epidemic, and that immunosuppression may not have been advanced. Some clinicians have decided that the higher proportion of HIV-related tuberculosis with negative smears requires enhanced clinical suspicion, and that in the

presence of radiological abnormalities not explained by other causes, empiric therapy for those HIV positive may be justified in view of the high risk of tuberculosis in HIV-infected individuals.[74, 95]

4.7 Case Finding

Diagnosis of pulmonary tuberculosis depends on identification of clinical features, and confirmation by sputum microscopy. An important question is whether it is more effective to control the disease by actively seeking out suspects (active case finding), or whether health services should wait for patients to present with their symptoms (passive case finding).

4.7.1 Passive case finding:

A series of studies in Kenya showed that actively looking for patients suspected of having tuberculosis by various methods using community leaders, or household members attending clinics, did not identify more cases of disease than had already presented to a health service with symptoms at some stage.[97] An earlier study showed that it was "epidemiologically and economically justified to base tuberculosis control programmes on the persons who seek assistance because of worry over symptoms". At a later stage more extensive case finding could be used.[98] A case finding study from Thailand reported a "rapid village survey", involving self-presentation after health education, which proved as efficient in finding cases as the more expensive household survey.[99]

Both developed and developing countries have agreed to the recommendations of the IUATLD (International Union Against Tuberculosis and Lung Disease) and the WHO that passive case finding methods be employed universally.[28] Issues of importance are delays on the part of doctors (and other health workers) and patients.[100]

Health worker delays are reduced by vigilance and awareness at primary and other levels of care.[68] The series of Kenyan studies describe how tuberculosis disease was missed many times in symptomatic patients because health workers in peripheral clinics neglected to investigate 80% of such cases.[80] Delays occur in hospitals too. In an academic hospital in Malawi there were long delays between admission of patients and their diagnosis and initiation of treatment, resulting in concerns about nosocomial tuberculosis transmission.[78]

In Kenya, the proportion of outpatients with diagnosed tuberculosis who lived within 9 miles of the hospital was 41% compared with 15% for outpatients living further away. This suggested the need to improve case finding in peripheral clinics, which would require motivation, training and supervision, attention to clinic staff's work load, to the logistics of supplies, and to improved communication within the district.[97] However, the failure of the peripheral services to identify and investigate suspect tuberculosis cases may be interpreted as the need for these functions to be performed in district hospitals.[80] Issues of decentralisation of diagnosis and management of patients with tuberculosis will be explored in chapter 18.

Patient delays are often a problem, often not the fault of individuals. Many forces operate to delay the prompt presentation of patients for medical care when they develop symptoms. Health services must be accessible and acceptable for passive case finding to be successful in controlling tuberculosis.[28, 101] Such needs have led to the proposal that tuberculosis services be incorporated within the primary care network within a community.

The relationship between health service and patient delays and patient treatment adherence will be discussed in chapter 8. Issues on the integration of tuberculosis services at primary care level will be reviewed in chapter 10.

4.7.2 Active case finding:

Active case finding is most usefully employed in high risk groups within populations in order to prevent disease. Groups thus identified include child contacts of adult tuberculosis patients, those infected with HIV, those with radiological fibrotic lesions, silicosis and those with other known risk factors.[100] The purpose of active case finding in each of these examples is to institute chemoprophylaxis. Chapter 5 covers this subject.

CHAPTER 5

PREVENTION OF TUBERCULOSIS

This chapter will consider:

General prevention

Specific chemoprophylaxis for:

Child contacts of smear positive persons

Tuberculosis-infected individuals

HIV-infected individuals

Individuals with silicosis

5.1 General prevention

Tuberculosis can be prevented if people are not exposed to the risk factors that predispose to infection and disease. Many of the risks of exposure and infection are associated with poverty and poor living conditions and standards. Improvement of economic status, education, housing and health services will help to reduce the incidence. Nine of ten commitments listed as requirements for tuberculosis control were concerned with measures directed against the disease; the tenth described the need to address poverty and to promote "....a much wider commitment internationally to reducing the economic inequalities which allow tuberculosis to remain such a preventable scourge all over the world".[102]

The most important preventive measure available to health workers is the cure of smear positive individuals in order to stop transmission. A specific preventive health intervention is vaccination with BCG, the effectiveness of which has varied in a number of studies in different parts of the world.[103] BCG vaccination does not feature in the recommended tuberculosis control programmes, and will not be discussed further in this thesis.

5.2 Specific prevention (CHEMOPROPHYLAXIS)

The role of chemoprophylaxis is controversial and differs in different situations. A review of several studies which examined the effectiveness of chemoprophylaxis (preventive therapy) concluded that this intervention reduced the incidence of tuberculosis in risk groups by a wide range of 25% and 92%.[104] Another review, of 20 controlled trials of the effectiveness of chemoprophylaxis with isoniazid (INH), described a weighted reduction in disease of 60%.[105]

5.2.1 Child contacts:

Evidence for a higher risk for contacts under the age of 15 years exposed to smear positive household individuals, compared with other age groups, was provided by studies in Canada between 1966 and 1971.[16] A risk higher than in other age groups remained if the index case was culture positive. The conclusions were that risks of infected individuals developing disease were age, time since infection and bacteriological status of the source. Half the 10% lifetime risk of disease occurs in the first 5 years of life.[29] Chemoprophylaxis for young children exposed to smear positive disease may be a cost-effective intervention.[28]

These facts form the basis for the recommendations by some national programmes that children under the age of 5 years who are contacts of infectious cases should receive chemoprophylaxis in order to prevent progression to disease.[106]

5.2.2 Individuals infected with tuberculosis:

In North America preventive therapy is widely used for persons infected with tuberculosis, based on recommendations of the American Thoracic Society and US Centers for Disease Control.[107, 108]

Research is required to find drugs as effective as isoniazid, but which require shorter

administration periods and have fewer side effects.[109]

A World Health Organisation (WHO) expert committee has declared that preventive treatment is not suitable for mass application in a community health programme, and is in fact, irrational even for special risk groups, unless high cures for infectious cases are being achieved.[90] Any benefits of preventive treatment may be outweighed by the disadvantages of diverting resources from the essential aim which is the cure of infectious disease. The diversion of funds and personnel away from smear positive patients has been similarly argued in other reviews.[110]

Other practical reasons for not implementing this measure in developing countries are the fact that the widespread use of BCG vaccination has decreased the ability of tuberculin skin tests to identify infected individuals, and that in such countries there is a high likelihood of disease which would be inappropriately managed with the monotherapy of chemoprophylaxis.[111]

5.2.3 HIV-infected individuals:

It has been shown that 10% of HIV-positive tuberculosis-infected individuals develop tuberculosis disease per year, and that the disease could be prevented by a course of isoniazid for one year, similar to the preventive effect in HIV-negative persons.[30,112] However a recent randomised controlled trial using isoniazid preventive therapy in HIV-infected adults did not show a statistically significant protective effect of daily isoniazid for 6 months when patients were followed for a median of 1.8 years.[113] The lack of effect was partly explicable by the high annual risk of infection in Africa where the study was carried out, such that newly acquired infection is a risk for all persons, HIV-infected and uninfected, as soon as preventive therapy was stopped.

Recommendations from the Centers for Disease Control and Prevention and others in 1991

were that chemoprophylaxis be offered to all anergic HIV-infected persons in populations where there is a prevalence of HIV-infection of 10% or more.[114, 115]

Grzybowski argues that preventive therapy for dually infected persons could be considered simply as early treatment of tuberculous disease, since the risk of tuberculosis in such people is 50%.(116) Knowing whether disease is due to reactivation or to new infection would help with decisions about prophylaxis, as the former would be protected by chemoprophylaxis, but the latter would not.

In developing countries, the increased number of infectious cases caused by HIV will gradually increase the risk of infection. This could be averted by efficient case finding and high cure rates of smear positive cases.[40, 61] However preventive therapy may be appropriate for identified HIV-infected individuals.[43, 117] Workers in developing countries, concerned about patient non-adherence to preventive therapy and costs to health services, are not confident that preventive therapy will have any impact on tuberculosis control, nor that it would be possible or cost-effective to offer it to all HIV-infected persons.[118] Further research is needed to measure cost-effectiveness and feasibility.[119]

A joint IUATLD/WHO statement summarises the still controversial issue, but provides practical guidelines.[120]

There is insufficient information to recommend universal preventive therapy for co-infected individuals. Programme implementation should only be considered when targets of 85% cure and 70% detection of smear positive patients are achieved, and where voluntary counselling and testing for HIV-infection is available. HIV-infected persons should have tuberculin skin testing. If this is positive, a suggestive chest radiograph and symptoms should lead to a sputum microscopy examination. In the absence of active tuberculosis, such persons should receive isoniazid prophylaxis for 6-12 months.

Arguments remain, that for developing countries this strategy may not be a feasible public health measure, as it would divert resources from the primary target of control - the active cases of disease, and would entail HIV testing, too costly for most countries.[61, 110]

5.2.4 Individuals with silicosis:

A review of early studies could not draw firm conclusions about chemoprophylaxis in individuals with silicosis, as patient numbers were small.[49] However one study did show that INH given to silicotic individuals resulted in a 14-fold decrease in new cases of tuberculosis compared with those for whom no INH was given.[121] A Hong Kong study of 679 silicotic men showed that drugs (INH or rifampicin alone for 24 and 12 weeks respectively, or the two in combination for 12 weeks prevented disease, in fact halved the rate of development. However disease still occurred at unacceptable rates, and the preventive effect was not optimal.[122] No preventive effect was demonstrated in an intervention study of 382 South African gold miners with silicosis, randomised to receive a rifampicin-isoniazid-pyrazinamide combination or a placebo for 3 months.[123] It was postulated that a significant proportion of the mycobacteria must have remained dormant during the treatment period of three months.

THE MANAGEMENT OF TUBERCULOSIS

The management of tuberculosis is dependant on the successful application of drugs of known efficacy, for the period of time determined from studies to prevent the highest proportion of relapses. Management is unlikely to be successful unless the factors relating to patient treatment adherence are considered and adjusted for. Three chapters will cover the essence of management:

Chapter 6 CHEMOTHERAPY

Chapter 7 CONTROL PROGRAMMES

Chapter 8 TREATMENT ADHERENCE

CHAPTER 6

CHEMOTHERAPY

This chapter includes:

- *Drugs against tuberculosis*
- *Recommended drug regimens*
- *Drug combination tablets*
- *Monitoring of treatment*
- *Measurement of treatment outcomes*
- *Costs and cost-effectiveness*
- *Chemotherapy in HIV-infected patients*
- *Chemotherapy in patients with silicosis*
- *Management of drug resistant tuberculosis*

6.1 Drugs against tuberculosis

6.1.1 History:

Until the discovery of drugs active against *Mycobacterium tuberculosis,* risk factors in the hosts and the immune response were the focus of attention. Patients were told to rest, eat good food and to live without stress. Medical treatment was restricted to surgery. Such methods became irrelevant with the availability of potent chemotherapy which shifted the battle to that between the organisms and the drugs.[124] Modern chemotherapy started with the discovery of streptomycin in 1944 and its use as a single drug. This created resistance since this monotherapy selected out pre-existing streptomycin-resistant mutants.[125] The first report on a controlled trial of streptomycin was in 1948, followed by others on the 3 drug regimen of streptomycin, para-amino-salicylic acid (PAS) and isoniazid (INH), the last two introduced in 1949 and 1952 respectively. The bacteriological basis for using triple therapy to prevent drug resistance was elucidated by Mitchison.[124]

A course of treatment lasting 2 years or more, using the drugs in divided doses several times a day, resulted in high cure rates and low relapse rates.[126 127] However treatment was expensive and difficult, for patients and for health services, because patients required hospitalisation for long periods.

Several studies proved the effectiveness of intermittent twice-weekly, supervised therapy using isoniazid and streptomycin or isoniazid and p-aminosalicylic acid.[128, 129] The Madras study,[128] showed that once-weekly administered drugs resulted in a higher proportion of failures, and could not be recommended, although good results were achieved in patients shown to be slow isoniazid inactivators.

6.1.2 Rifampicin-containing regimens:

In 1966, a new bactericidal drug, rifampicin, was introduced. One of the first trials demonstrating the effectiveness of regimens which included this drug, was conducted in 1973 by the British Medical Research Council.[130] Fox, reviewing trials from East Africa and Hong Kong, concluded that a six month regimen was optimal for smear positive patients.[131] Using 4 drugs (rifampicin, INH, PZA and streptomycin) bacteriological relapse rates for nine, six, four and a half to five and three month regimens were 1%, 1%, 3%, 12% and 13% respectively. The 6 month period of treatment has become known as the "short course" regimen. It was used in Tanzania in 1982, with resultant cure rates of 77%, or up to 90% if patients who died, or were transferred elsewhere were excluded, and those absconding assumed to have converted. Increases in cure rates of 25-30% over the "standard" treatment without rifampicin were recorded.[67]

Fox concluded from these results that extending the period of 4-drug chemotherapy beyond

6 months was not worthwhile, since relapse rates were so low that extensions would mean unnecessary treatment for 98-99% of patients.[85]

The importance of supported treatment was emphasised: "it is paradoxical to insist on the importance of 100% success with primary chemotherapy and to use self-administered chemotherapy as a means of achieving it". Thus the concept of directly observed therapy currently emphasised by the WHO for all tuberculosis programmes is not new. In addition, Fox's review commented on the necessity for organisation of adequate supplies of drugs and stock control, and for the lowest possible prices to ensure wide availability.

It was estimated that short-course chemotherapy would reduce the annual risk of infection in Tanzania by 4-5% per year to a level of 0.5% within 15 years. This would reduce by half those infected and diseased by the year 2000, such that the disease would no longer be a major problem.[132]

6.1.3 Effects of different drugs:

Rifampicin has the most powerful early sterilizing action of all the anti-tuberculosis drugs, acting rapidly on all types of mycobacterial populations. Pyrazinamide (PZA) has a similar early sterilizing action, acting in an acid medium against intracellular bacilli, with a high grade early sterilizing action useful for the initial phase of treatment. Isoniazid, being highly bactericidal, acts against the rapidly growing populations of organisms. Streptomycin's action is against rapid dividers and has less sterilising and bactericidal activity. Ethambutol and thioacetazone are bacteriostatic drugs with a role in the prevention of resistance. Each drug has an independent sterilizing, bactericidal and resistance prevention role which contributes to the combined effect.[133, 134]

Successful tuberculosis treatment depends on much more than the science of chemotherapy.[135] Some of the literature on operational aspects of programme management and patient adherence to treatment will be reviewed in chapters 7 and 8.

6.1.4 The effect of good and poor treatment programmes:

Estimates are that without treatment 50% of patients will die within 5 years, 30% will recover and 20% will remain chronic excreters of bacilli.[59] Good treatment (individual therapy) can cure 90% of patients. Poor programmes, using "mass treatment" save lives, with cure rates of 60%, and survival rates of 25% who become chronic excreters. The latter can perpetuate the tuberculosis epidemic, with many being resistant to first-line drugs.[56]

6.2 Recommended drug regimens

Recommendations for treatment regimens for national control programmes have been developed by the WHO and the IUATLD. Guidelines provide information on effective regimens, alternative regimens if the more expensive drugs (notably rifampicin) cannot be provided, alternative timing of doses using intermittent regimens three times per week, and on possible side effects. They include the duration (6 months for regimens containing rifampicin), the phases (intensive and continuation), and the dosages.[136, 137] The regimens are summarised below:

New smear positive patients, smear negative patients with extensive disease, and new extrapulmonary disease:

Initial two months:
four drugs (rifampicin, INH, PZA and Ethambutol or streptomycin)
Continuation phase:
four months of rifampicin and INH
OR (for countries for whom rifampicin is too expensive)
six months of INH and ethambutol

For severe forms of tuberculosis, meningitis, miliary and spinal disease, a 7 month continuation phase is recommended by some.

Retreatment regimen for patients who have relapsed, failed the first course or interrupted their treatment:

Initial three months
two months of a five drug regimen (streptomycin, rifampicin, INH, PZA, ethambutol)
followed by
one month of four drugs as for the first two months, but without the streptomycin
Continuation phase of five months:
five months of INH, rifampicin and ethambutol

Thiacetazone has been in use as an alternative to ethambutol in the continuation phase when rifampicin is not used. The use is controversial because of the risks of severe side effects in HIV-infected persons. The debates will be outlined later in this chapter when treatment of HIV-infected tuberculosis patients is considered. (page 45)

Intermittent regimens with drugs administered two or three times a week have been shown to be as effective as when given five times a week or daily.[138, 139, 140, 141] These

regimens may be a useful option in situations where daily supervision of treatment is not possible, and where patient adherence is a problem. The WHO does not, however, recommend twice-weekly regimens because missed doses represent large proportions of total treatment, and can result in failure.[136] Doses for intermittent regimens are higher than for daily doses and side effects need to be monitored carefully.

6.3 Drug combination tablets

A number of studies have found treatment using tablets with drugs in combined form to be effective, to provide an easier option for patients and staff and supporters, and to avoid monotherapy.[139, 142] Results of two South African studies of rifampicin, isoniazid, pyrazinamide combinations showed these to be as effective as regimens in which the drugs were given individually.[143, 144] In a study from Singapore, the relapse rate was slightly, but not significantly higher when combination tablets were used.[145] However it is essential that bioavailability be demonstrated, and that drug companies be compelled to meet the quality standards of international expert groups.[146, 147]

6.4 Monitoring of treatment

Recommendations for therapy include bacteriological monitoring during short-course chemotherapy. The priority target for treatment is smear positive patients, whose response to treatment requires measurement of the smear status after two months of treatment in order to assess progress, with extension of the initial phase by 1 month if the smear remains positive. Further smear testing is done at the end of a course of treatment, to establish if cure has been achieved.[136]

Sputum smear conversion occurs in 75% of patients after 2 months of treatment, with

results at that time said to be predictive of later bacteriological results.[148] Sputum culture conversion at two months is also a reliable measure of sterilizing activities of drugs, non-conversion being predictive of treatment relapses.[149]

6.5 Measurement of treatment outcomes

There are six possible outcomes of treatment of pulmonary tuberculosis which are recorded in the registering system developed by the WHO.[136] These are:

Cure	*bacteriological conversion at the end of treatment, and at least once during treatment.*
Completed	*treatment course completed, but no final smear results*
Failed	*smear remains positive at the end of treatment*
Died	*died during the course, of whatever reason*
Interrupted	*patient interrupted the course for 2 months or more*
Transferred	*patient was transferred to another treatment point*

6.6 Costs and cost-effectiveness

The cost (to the IUATLD in 1995/96) of short-course chemotherapy using the 8-month rifampicin-containing regimen is about US$18, and that of the previously used "standard" 12-month, non-rifampicin therapy containing thioacetazone is about US$8. For many countries without hard currency or donor support, there is no option but to use the standard regimen.[150] Short-course chemotherapy was found to be more cost-effective for each of the outcomes measured, namely cures and deaths averted.[28] Retreatment needs were three times greater for the standard treatment and death rates twice as high. In addition expectations were that the higher cure rates in short-course regimen patients

would result in a decline in the risk of infection, and would limit drug resistance. Thus short-course chemotherapy has been described "an excellent investment relative to virtually any health intervention".

Analysis of programmes in Malawi, Mozambique and Tanzania showed that treatment of smear positive tuberculosis costs $20 to $57 (in 1989 terms) per death averted. The cost per discounted year of life saved was calculated to be $1 to $3, making this intervention one of the most cost-effective known.[151]

Two clinical categories of patients bear special consideration regarding treatment, those who are HIV-infected, and those who have pre-existing silicosis.

6.7 Chemotherapy in HIV-infected patients

Tuberculosis in HIV-infected individuals is now common. The important questions to be asked is whether the treatment regimens are as effective as in non-HIV-infected people, and whether relapse rates are higher.

Case fatality rates in HIV-infected patients are higher. A study in Nairobi described a 20% higher case fatality in HIV-infected patients one year after tuberculosis treatment, and attributed this mainly to HIV-related illnesses.[152] A study from Zaire also showed significantly higher case fatality rates attributable to HIV-infection, both during treatment and after completion of treatment. The after treatment higher fatality rate was attributed to relapse. One year after, treatment relapse rates were three times higher in HIV-infected patients compared with HIV-negatives. Treatment used was the "standard" 10-month regimen using isoniazid, thioactezone and streptomycin. Patient compliance was less in the HIV-positive group and

would have been partly responsible for the higher relapse rate. There were similar treatment failure rates in HIV-positive and HIV-negative cases.[153] A three times lower adherence rate in HIV-positive patients was described from South Africa.[154] Higher relapse rates in HIV-positive individuals were found in a study from Nairobi.[155]

A review of treatment regimens which include rifampicin has shown them to be almost 100% effective in HIV-positive and HIV-negative groups, with recurrence rates only slightly higher in the HIV-positive patients.[156] Any change in treatment policy for HIV-positive patients would require that all tuberculosis patients have HIV tests. This would have cost and other resource implications which may make such testing unfeasible for developing countries who bear the brunt of the dual problem. The CDC recommendations of 1987 were that HIV-infected tuberculosis patients be treated for a minimum of nine months, or for six months after culture conversion, as long as rifampicin and isoniazid were included in the regimen.[157] Since that time, several studies have shown a 6-month course to be effective.[158, 159]

The 1997 recommendations of the WHO are to administer the same short-course therapy to HIV-infected and non-infected tuberculosis patients, but replacing thioacetazone with ethambutol. Streptomycin should be avoided if resources for sterilising injection equipment are not available.[136]

Thiacetazone is a drug which has been useful in tuberculosis treatment in countries which are not able to afford the six month short-course containing rifampicin. These are the countries in which HIV-infection is most common, which is unfortunate because serious epidermal necrolysis can occur in HIV-infected persons receiving this drug.[160] The expense of using ethambutol instead is serious problem. Calls to halt the use of thiacetazone,[161] have been

countered with reports that reactions are less common than first thought,[150, 162] and the suggestion that thiacetazone does offer an affordable option.[163] Testing all tuberculosis patients for HIV-infection, and using a more expensive drug for those testing positive is expensive for poor countries. An appeal is made for the continued use in countries where economic constraints are realities, and for whom the usefulness of the drug in preventing resistance is known.[150]

6.8 Chemotherapy of patients with silicosis

Silicosis is not uncommon in male tuberculosis patients in South Africa, which justifies a short review of treatment effectiveness in such patients. Such patients are predisposed to disease because silica-exposed macrophages have been shown experimentally to be incompetent.[49] Delayed sputum conversion on treatment and higher relapse rates have been postulated.[49] In a controlled trial in South African miners of 94 silicotics and two matched-pair control groups without silicosis, there was no higher relapse rate in tuberculosis patients with silicosis treated with a six month course. Short course therapy was judged equally effective for cases and controls.[164] Another study on South African gold miners evaluated the relapse rate after treatment of 2776 men. It showed that extensive disease affected the relapse rate, but that the presence of silicosis did not.[165] A study from Taiwan on 59 silico-tuberculotics who had a nine month treatment regimen suggested that treatment was effective, although less effective than in non-silicotics (but no controls were studied).[166]

A small, but not significant decrease in relapse rates resulted after tuberculosis treatment in men with silicosis compared with those without, in a more recent study report of 549

South African gold miners, 167 of whom had silicosis.[167]

Definite conclusions are difficult to draw at this stage. Research is on-going.

6.9 Management of drug resistant tuberculosis

6.9.1 Pathogenesis of resistance:

Resistance of mycobacterial organisms to a drug is due to a mutation in the gene that encodes the target protein bound by the drug. Exposure to a drug does not induce the mutations, but allows mutants already present to flourish by destroying drug-sensitive organisms. Without the presence of a drug, resistant organisms arise spontaneously, at rates that are different for each drug. The larger the bacillary load in a patient, the greater the chance of mutant resistant bacilli to different drugs.[168] The chances of an organism being resistant to more than one drug is the product of the resistance rates for each drug. The use of two or more drugs in appropriate doses lowers the probability.

The first phase of tuberculosis drug resistance was experienced when streptomycin was used alone in the 1940s, the second when isoniazid resistance appeared, and the third, current phase, when resistance to isoniazid and rifampicin (by definition multi-drug resistance) has become increasingly prevalent.[169]

Causes are the use of single drugs, unreliable combinations, repeated additions of additional single drugs in an attempt to improve patients' responses, irregular drug supplies, ignorance on the part of doctors, and of patients, who use monotherapy.[170]

Acquired resistance refers to that developed by individuals during inappropriate treatment. Primary resistance results from transmission from those who have the infection with resistant strains.

6.9.2 The size of the multi-drug resistant (MDR) problem:

Accurate measures of MDR tuberculosis are not available for most countries. The problem in the developing world has been difficult to assess because of non-standard laboratory methods and selection bias of patients reported.[171] It is likely to be a growing problem.(39) The global situation has been reviewed by Cohn et al.[172]. Patients who have had previous treatment for tuberculosis may constitute up to 50% of all patients being treated when a control programme is implemented. Acquired resistance may be as high a 50-80% in these cases. Once a control programme has been operating well for a number of years, the proportion of old, previously treated cases drops to around 10-20% of the total, and acquired MDR is around 4-10% of those cases. Primary MDR is more common in situations where control programmes were poor, where it may be 7.5% of new cases, whereas it is uncommon, 1% or less, when good programmes have been implemented for some years. National surveillance systems for drug resistance are currently being instituted in many countries, so that the emerging problems can more accurately be measured.[173]

6.9.3 The relationship between HIV and MDR:

Multi-drug resistance in association with HIV infection has not yet been described in developing countries,[62] although it has been reported from the United States.[174] Several outbreaks of MDR in New York hospitals in the late 1980s involved 82 cases of MDR tuberculosis and gave cause for alarm. At least 85% were HIV-infected, suggesting that HIV-infection was associated with resistance. These outbreaks were responsible for focusing renewed attention on tuberculosis in the United States.[175, 176, 177] Eleven thousand patients were diagnosed with tuberculosis in New York City during two two-year periods 1991-92 and 1993-94. The decline in incidence of MDR of 44% noted between the two

periods was ascribed to better rates of completion of treatment, and was termed "the end of the beginning" and "turning the tide" of tuberculosis and MDR in the USA.[178, 179] A study of 100 patients with MDR demonstrated that patients were predominantly minority males under the age of 40 years, jobless, homeless, drug abusers and HIV-infected. Thus it appeared that the HIV association was not directly causative, but one of several factors in the social environment of the patients involved.[180]

Another reason for the association between MDR and HIV-infection has been described by Enarson. The time between poor treatment and the emergence of primary resistance may be about 15 years. HIV infection shortens this period to around 10 years, because the duration of many of the stages from improper treatment to acquired resistance, then primary spread to contacts is reduced. Thus the prevalence of resistance would be higher in HIV-infected persons, and may account for the association without any direct impact of HIV on the development of resistance.[181]

6.9.4 Treatment and Prevention of MDR:

All drug resistance (apart from the use of unreliable drugs in some countries) is due to bad doctoring and is therefore avoidable.[182] The WHO retreatment regimens for persons with active disease who have received a course or part-course of treatment in the past can cure 90% of cases of acquired resistance to isoniazid and/or streptomycin. Between 60% and 80% of MDR cases, failures and relapses after retreatment regimens can be cured by the WHO recommended second-line drugs given in specialised units.[183]

WHO recommendations provide details on the drugs for MDR cases and optimal treatment settings, and emphasise that the top priority is not management, but prevention of MDR with implementation of short-course chemotherapy for all new smear positive cases.[184]

CHAPTER 7

TUBERCULOSIS CONTROL PROGRAMMES (TBCPs)

This chapter includes:

TBCP principles

Directly-Observed Therapy Short-course(DOTS)

Hospitalisation of patients

The impact of HIV-infection on tuberculosis control

Doctor and other health worker compliance

A review of different country control programmes

Integration of TBCPs within primary health care

7.1 Tuberculosis control programme principles

The existence of the means to diagnose and treat tuberculosis does not necessarily imply that health services reach those in need. Principles for implementing tuberculosis control programmes have been drawn up by the International Union against Tuberculosis and Lung Disease, and the World Health Organisation.[68, 185] The prime objective of control programmes is to improve the cure rate of tuberculosis patients, particularly that of smear positive patients, to 85% in developing countries and to 95% in developed countries. The second objective is to detect 70% of cases through available health service networks.

A control policy "package" includes the following components:[186]

i) government commitment to a tuberculosis programme

ii) case detection through passive case-finding

iii) administration of standardized short-course therapy for at least all confirmed smear positive cases by directly observed administration

iv) a regular drug supply of essential tuberculosis drugs

v) a standardised recording and reporting system that allows evaluation of treatment results

The recommendations include the development of a microscopy network through which individuals with suspected disease can be diagnosed. Reasons why microscopy services based at peripheral levels in a district might not be appropriate have been described in chapter 4, page 23. Wherever they are situated, communication between clinics and their referral laboratories must be ensured.[185]

7.2 Directly-Observed Treatment Short-course (DOTS)

7.2.1 Definition and History:

The DOTS strategy, proposed to ensure patient adherence, is treatment which is directly observed by a person other than the patient. The idea is not new to the 1990s. Fox, in 1958, suggested that "less fundamental" than the chemotherapy being used was the regularity of self-administered treatment.[187] This led to further work which showed that daily supervision of treatment improved regularity.[188]

Sbarbaro has reviewed the use and success of DOTS in ten studies between 1966 and 1977 with treatment successes one year after treatment ranging from 79% to 100%.[189] Subsequent developments in supervised treatment have been reviewed by Bayer and Wilkinson, who describe experiences with supervision of treatment in Madras, Hong Kong, England, and the United States.[190] Although patient treatment completion rates remained poor in many countries, supervised treatment was not widely implemented until the early 1990s.

7.2.2 Studies of effectiveness of DOTS:

During the period 1975 to 1980, patients in the USA who had histories of failed treatment

were successfully managed with supervision at clinics by nurses.[191] Methods of implementing DOTS have varied from the use of health workers at health facilities to the enlistment of volunteer non-health workers. A study in Denver, USA, in the 1980s reported less than 10% of patients lost during supervised treatment.[192] Another study compared outcomes of 407 episodes of "traditional" treatment without DOTS with those following DOTS treatment for 581 patients during two periods 1980-1986 and 1986-1992. Primary, acquired and multi-drug resistance levels were significantly lower in the DOTS group, as were relapse rates.[192] From Kenya have come reports of improved successful treatment rates after implementing supervised treatment in 'manyatta' villages constructed for tuberculosis patient under treatment, where food and shelter as well as daily treatment are provided for nomadic populations previously shown to have great difficulties in completing treatment.[193] This is an example of an intervention that meets a local need. Another example of the effectiveness of DOTS is from Nepal where an alarming rate of interrupted treatment (60-80%) and of drug resistance prompted the use of an intermittent regimen supervised by clinic staff. With DOTS the cured and completed rates for smear positive patients improved to 83%.[194] In Bangladesh, a community health worker programme was successfully implemented (the BRAC system).[195] Treatment supervised by community volunteers in Cape Town was not found to affect the adherence of adults, but did improve that of pre-school children.[196]

DOTS has been described as the only effective approach for difficult problems of drug addiction and alcoholism, homelessness, psychiatric illness and indifference of patients.[192]

7.2.3 Costs and cost-effectiveness of DOTS:

DOTS is a cost-effective measure as shown by the prevention of treatment failure, and by the savings on expensive investigations to monitor self-administered regimens.[197] A 13%

saving was calculated in a study in Denver by Cohn et al.[140] Sbarbaro found that the costs of "standard" regimens, in which patients are initially hospitalised, then attend monthly, were less than those of DOTS administered by a professional.[189] In a rural South African context, different strategies were costed. It was found that a short period in hospital followed by community-based DOTS cost half that of 2 months' initial hospitalisation followed by health worker-supervised DOTS, nearly one third the cost of sanatorium-based care for the full duration of treatment, and 25 times less than a previous regimen of 4 months in hospital and a further 4 months unsupervised out-patient drug taking.[198]

7.2.4 Universal use or flexibility:

It has been suggested that the serious and worsening tuberculosis problem with literature reports of an overall one third of patients non-adherent to their treatment, justifies the use of entirely intermittent directly-observed treatment for all patients.[197] Arguments against this cite the difficulties in persuading patients to attend a clinic two or three times per week, while expressing concern that "outreach" staff (non-professionals) cannot substitute for public health nurses. However the plea is made for tailoring treatment to the individual patient.[199] It is said that DOTS is an imposition on patients and too resource intensive for health services. Health service staff can be substituted, as demonstrated from a rural district in South Africa, where 89% of surviving patients completed their 6 month twice weekly DOTS-administered course. Patients' attendance at supervisors was monitored by regular health staff visits to these supervisors who included shop-keepers, employers, or health service staff, depending on patient convenience.[200] Significantly more patients supported by lay community members completed treatment in this same setting, compared with those supported by health workers (85% and 79% respectively).[201] In New York community supervisors were workers in soup kitchens, shelters, HIV and substance

abuse centres and parole programmes, all able to relieve health workers of the function.[202] Many states of the USA have legal powers to protect the safety and health of the public, and can confine patients, should they be shown to have active tuberculosis which presents a danger of spread to others. Although DOTS is described by one author as restrictive and "gratuitously annoying", it is acknowledged as preferable to involuntary confinement. It must be admitted that both interventions focus on the victims of social neglect rather than on the neglect itself.[203]

The potential for community-based non-government organisations to impact on tuberculosis is emphasised in a review of Southern African community care organisations. The proposed model for the roles of such groups includes DOTS.[204]

Patient acceptance for DOTS is paramount. There has to be individualisation of treatment for every patient, depending on settings and social circumstances, but not at the expense of public health. Bonds do develop between patients and their supervisors, who may not be part of the health service, yet able to perform the tasks adequately. The solutions to treatment problems must lie within a multi-pronged approach with DOTS, patient education and combination tablets.[205]

7.2.5 DOTS as a strategy:

The WHO has hailed DOTS as the "biggest breakthrough of this decade" and the "single most important development in the fight against (tuberculosis)".[206] None of the completed intervention trials have examined DOTS, the apparent success of which is based on poorly controlled research, in which selection biases may have led to optimistic conclusions about the effects. It is not easy to evaluate DOTS, meaning supported treatment, without measuring the influence of confounders, since this strategy is usually integral to good control programmes. Multiple logistic regression would be useful in this regard.

Programmes in which DOTS feature still require substantial effort to manage tuberculosis services.[207]

DOTS in summary:

In summary, it has been shown that community-based support for patients can be organised, that the process need not drain resources from health services, and that this process can work, although research needs to confirm this. The recognition that untreated, non-compliant patients constitute a grave risk to public health, requiring some supportive measure to ensure pill taking, has led the WHO, IUATLD and the United States Advisory Council for the Elimination of Tuberculosis to recommend DOTS.[67, 117, 136, 208] *However DOTS is not a magic cure-all, but a strategy within control programmes for facilitating patient adherence.*

7.3 Hospitalisation of patients

The emphasis of modern management of tuberculosis is on community-based, ambulatory treatment. However there are clinical and social indications for hospitalisation which require policies for efficient utilisation of hospital care, with avoidance of delays which could lead to increased transmission of disease.[209, 210]

7.4 Impact of HIV-infection on tuberculosis control

The critical importance of good national tuberculosis control programmes, and of the impact of HIV-infection on tuberculosis, was highlighted by a review of trends in case rates in 20 Sub-Saharan countries before and after 1985.[47] Rates before 1985 in 10 selected countries were declining. In all 20 countries the rates had increased by an average

of 7% per year after 1985. Rates in countries with high HIV seroprevalence ratings were double those of countries with lower HIV figures, but for all levels of HIV seroprevalance, the annual increase in case rates was inversely related to the quality of the control programmes. The review concluded that additional investments in tuberculosis control programme quality in Africa could lead to reductions in morbidity from this disease, even in the era of HIV. This endorses the statement of Styblo in 1990 that in the era of HIV, good tuberculosis control programmes can lead to reductions in disease, and are the most decisive factors in containing the problem.[40]

7.5 Doctor and other health worker compliance

Patient adherence to recommended treatment is crucial for the successful completion of a course of treatment. Chapter 8 is devoted to the literature on this topic.

However another important factor in success is compliance of all health workers with diagnostic and treatment policies. Those involved are decision-makers who establish policy and organise resources, those at the next levels who supervise control activities, and those who correctly manage individual patients by prescribing recommended regimens. Chaulet states that compliance or non-compliance are the consequences of people "who do or do not do the work for which the community pays them".[211] This theme had been expounded previously by Fox who describes the need to influence physicians' prescribing habits through dissemination of information in publications, in stated government policies, and through educational activities.[212] Several studies have shown that doctors do not use recommended drugs. In Korea, 89% of doctors questioned were not using recommended regimens,[213] in Pakistan the figure was 68% of general practitioners.[214] A group of patients in Hong Kong with diagnosed disease, was either incorrectly treated or treated for

an inappropriate period of time by private practitioners.[215] Studies from developed countries similarly described poor prescribing by doctors for treatment or preventive therapy.[216, 217, 218] The problems have been related to the professional arrogance resulting from training of doctors to make confident decisions about patient care, and to the desire of doctors in some countries to retain private patients who pay.[219]

7.6 A review of control programmes of different countries

A surveillance project was set up by the WHO in 1995 to examine control programme implementation.[220] Countrywide WHO control strategies were being implemented in 39 of 180 responding countries, representing a 23% global population coverage by the strategy. The estimated worldwide case detection rate of new smear positive cases was 35%, and there were 76% successful outcomes reported from countries using the strategy, compared with 42% successful outcomes in countries not using these strategies. Included in the success stories were countries which had had support from WHO and IUATLD, namely China, Tanzania and Malawi. Others were Morocco and Peru. In Sub-Saharan Africa up to 12% of patients had interrupted treatment and 5-6% had died. Conclusions were that higher cure rates were achieved by countries which had adopted the WHO strategy. However because such countries constitute a small proportion of the world, and because the case finding rates were low, the global impact of their programmes is small. Effective control will require wider coverage. The treatment outcomes of a number of countries whose control programmes have been reported are summarised in table 1 on pages 59 and 60. They show outcomes for smear positive patients, both new and retreatment categories. Those which use short course chemotherapy have shown successful outcomes. Those using standard 12-month courses have been less successful.

TABLE 1: TUBERCULOSIS TREATMENT OUTCOMES FROM STUDIES IN DIFFERENT COUNTRIES

COUNTRY (Reference)	YEAR(S) Number of pts.	TREAT-MENT**	OUTCOME - NEW SMEAR POSITIVE (%) *						OUTCOMES - RETREATMENT SMEAR POSITIVE (%) *					
			CU	C	I	F	D	T	CU	C	I	F	D	T
TANZANIA[221,222]	1982-88 25 000 new # 3 200 retr # 1990 5 500	SCC	82 79	 3	11 4	3 1	 8	5 5	73		13	4	7	4
CHINA[223]	1991-94 113 000	SCC	91-92		1-2	1-4	2-3	<1	79-84		1-2	6-18	6-18	<1
MOZAMBIQUE[224]	1985-88 4 200 new	SCC	70	8	11	2	2	8	69		16	4	4	8
HONG KONG[225]	1983 1600	SCC 3x/wk		59	7	?	4	?						
MALAWI[226]	1984-88 7 000 new 900 retr	SCC	87		2	1	7	2	89		4	3	3	
BRAZIL[227]	1984-87	SCC	76-83		11-15	1-2	3-4							
BOTSWANA[228]	1987-90 3 000	SCC	92		8									
THAILAND[229]	1981-90 929	SCC	76		0.4	-	5	19						
BENIN[230]	1983-88 2 800	SCC	81		10	2	6	1						

TABLE 1 CONTIN.: TUBERCULOSIS TREATMENT OUTCOMES FROM STUDIES IN DIFFERENT COUNTRIES

COUNTRY (Reference)	YEAR(S) Number of pts.	TREAT-MENT**	OUTCOME - NEW SMEAR POSITIVE (%) *						OUTCOMES - RETREATMENT SMEAR POSITIVE (%) *					
			CU	C	I	F	D	T	CU	C	I	F	D	T
NICARAGUA[231]	1984-89 2 500 new	SCC	78		13	2	3	5	62		22	9	4	3
NEPAL[194]	1990-93 411 new	SCC 3x/wk	69	14	13	2	1	2	59	8	13	5	5	11
KENYA[193, 232]	1985-87 996 1982-89	SCC daily DOTS Std	63	15	18	-	4	ex-cluded						
BANGLADESH[233, 195]	1984-88 187 1992-95 1 741	Std SCC DOTS	62		7		14	17						
INDIA[234]	1986-88 2 306 1051	SCC 2x/wk Std	42 34		2	1	7	2	89		4	3	3	
PERU[235]	1980 2 500	Std	47		41	6	4	-						
PHILLIPINES[236]	1985	Std 2x/wk	63		6	27	3							
ZAIRE[237]	1980	Std	62		21	11	2	4						

* outcome key: CU=cure, C=completed, I=interrupted, F=failed, D=died, T=transferred
** treatment SCC=short-course chemotherapy, Std= standard chemotherapy
# new= new patients, retr.= retreatment patients

Problems reported by many control programmes:

Health service delivery problems in rural areas included **shortages of staff, poorly motivated staff, inadequate supervision of staff, and no transport for case follow-up and delivery of drugs.** War in Mozambique had disrupted all services. In Nepal treatment of tuberculosis by **private practitioners was not according to recommended regimens.** Cohort analysis from tuberculosis registers was impossible in those countries which did not use the recommended recording system (Brazil, Hong Kong and Nicaragua). Constraining environmental issues cited were **unfavourable economic and political environments** (Bangladesh and Brazil), **overcrowded urban communities** where tuberculosis flourished (Brazil), and the existence of **nomadic rural** populations (Kenya).

The report from a district of India is an example of problems.[234] It described a low proportion of 3400 patients completing treatment, with only 41% who presented to a health facility adequately treated, and 22% of those remaining smear positive. The mortality rate (overall 28%), and smear positive rate after treatment (31%) were inversely related to the amount of treatment received, mortality of those who had had less than 50% of their treatment being 48% compared with 10% for those who had had 80% or more. Treatment was "supervised" for the 2300 patients on short-course treatment, but no "special measures" were used to increase compliance. This report precipitated several responses, one of which called the results "an unmitigated disaster", probably related to non-compliance of health staff and patients, to poor quality drugs and to lack of supervision of staff and patients.[238] It can happen that staff "are not doing the jobs to which they have been assigned and for which they are being paid".[239] Another response to the Indian report defended the concept of "culture-appropriateness" of compliance-inducing measures to understand reasons why in some developed countries compliance is poor, and why in some under-developed, poor

and socially marginalised populations, it is good. Technology alone is not enough; it must be within the acceptance pattern of the people and the health providers.[240]

Successful control programmes:

Reasons for successes were fairly consistent. Those countries with good outcomes cited **staff training and supervision** as important (Tanzania, Mozambique, Malawi, Thailand, Botswana). Several specifically mentioned the benefit of **expert assistance** from the IUATLD, as well as **donor funding** (Tanzania, China). **Integration** of tuberculosis services within other health services had been achieved in Botswana, Mozambique and Malawi, and were said to have contributed to better treatment outcomes. In Malawi and Tanzania positive results were attributed in part to the **political stability and favourable government policies** on health care. In Malawi, people's **agricultural self-sufficiency** eliminated the need for migration which made control programmes easier. In several countries there were **financial incentives** for those who facilitated cure of cases. In Bangladesh, money was paid to the 'shibika' who supported treatment, in China there was also a system of payment (for doctors) at completion of different stages of treatment. A consistent feature reported from good control programmes, and these included those in Tanzania, China, Thailand, Kenya and Nepal, was **directly observed treatment.** The Bangladesh report described the use of community health workers in the Bangladesh Rural Advancement Committee (BRAC) system in achieving 85% cure rates.[195] The workers, village women, are not paid, although they receive some profit from drug sales, are selected and trained for comprehensive basic health care at village level. More than 4 500 had been trained at the time of the report.

Suggestions have been made to modify control programmes, by simplifying chemotherapy regimens by removing some of the alternatives, and by reducing sputum smear monitoring tests which are difficult and resources intensive for rural health services.[241,242] Other authors have written in justification of tailored use of different regimens of different cost in order to prevent resistant disease, and of the during-treatment bacteriological monitoring as a valuable management tool for rapid evaluation of programmes.[243]

7.7 The integration of tuberculosis control programmes within primary health care services

Tuberculosis control programmes need well trained staff, able to implement the principles for effective treatment, efficient organisation of microscopy services and drug supplies, regular supervision and monitoring of practices, and the reporting and registering system. Theoretically it may seem that the objectives of a control programme could best be met by staff specifically dedicated for the purpose in a "vertical" or "selective" programme. In practice, tuberculosis is one of many health problems requiring intervention at the primary care level, so that the only practical, sustainable and cost-effective means of implementing a control programme is to integrate it within a comprehensive primary care package. Vertical and comprehensive approaches are not mutually exclusive, as there needs to be "a fruitful symbiosis of specialised knowledge and specific programme elements that go hand in hand with the efficient utilisation of an integrated health care system including functioning and community-based primary health care".[244]

Integration of tuberculosis services can only take place effectively in a functioning district health system. The discussion will continue in chapter 10 which will describe the district health system, and the place of tuberculosis services within this system.

CHAPTER 8

TREATMENT ADHERENCE

This chapter includes:

- *Introduction, definitions and predictors*
- *The health belief model and the patient perspective*
- *Socio-cultural factors*
- *Socio-economic issues*
- *Social support and community involvement*
- *Health service responsibilities*
- *Incentives*
- *Patient factors*

8.1 Introduction, definitions and predictors

The biological effectiveness of the recommended chemotherapy regimens are proven. The role of tuberculosis control programmes, and how they function within the context of countries' political, social and health service environments, have been discussed. Within programmes, the most important determinant of cure in tuberculosis is patient adherence.[28,211,212,245,246] The complexity and the size of the adherence issue is reflected in a vast amount of literature around the subject, including reviews of the health belief model and recommendations that health carers need to understand behavioural theory, results of interviews with patients and community members, and reports of studies of various designs which aimed to investigate factors associated with adherence and non-adherence.

Rene Dubos, the famous microbiologist, wrote in the 1940s,

> "tuberculosis is a social disease, and presents problems that transcend the conventional medical approach . . . its understanding demands that the impact of social and economic factors on the individual be considered as much as the

mechanisms by which the tubercle bacilli cause damage to the human body".[4]

It is paradoxical that over 100 years since the discovery of the *Mycobacterium tuberculosis,* tuberculosis remains a problem of great magnitude and we are forced to refocus attention on the social aspect of the disease and consideration of what it is that influences patient adherence to treatment. The problem experienced worldwide is ensuring that patients present to health services for treatment at an early stage in their disease, and that they take their full course of treatment. There has been a recognition of "social" issues, but the focus of treatment remains drugs.[247, 248, 249]

Compliance has been defined as the extent to which a person's behaviour (which includes taking medication) coincides with medical advice.[250] The term used in this thesis for patient treatment-taking according to recommendations is "adherence". This is in accordance with the suggestions that this is a more appropriate and less demeaning term than "compliance", which should be confined to the use by health workers of recommended policies and practices.[249]

Follow-up within a month of the start of treatment, or successful completion of the first month of treatment, have been found to be strong predictors of future adherence.[249,251] On the other hand previous treatment interruption is a documented risk for non-adherence.[252,253]

8.2 The health belief model and the patient perspective

The health belief model was developed to try to explain the phenomenon of non-adherence to preventive health behaviour. Becker's modified model to explain adherence behaviour

states that it is a result of a number of interacting factors.[254] These are patient motivation and willingness to accept medical advice, acceptance and practice of positive health promotional concepts, subjective estimates of susceptibility to disease and its severity, the extent to which the behaviour interferes with social roles, and perceived benefits and costs. Modifying and enabling factors described are attitudes towards and interaction with health staff, previous experience and source of advice and referral, structural entities of treatment accessibility and cost, duration of treatment, side effects, and some demographic factors. Treatment adherence is dependent on patient satisfaction. Thus there is justification and need for studying patients' perspectives of disease and health care, so that outcome may be improved.[255] There are a number of studies in the international literature which report results of interviews with individuals, and with groups, all of which aimed at providing information about beliefs and attitudes towards tuberculosis. Some of these will be reviewed in this chapter. Knowledge and attitudes were not compared with treatment outcomes in the majority of studies.

8.2.1 Stigma:

The stigma associated with tuberculosis has been a feature of the experience of patients from different communities worldwide. As examples are reports of patient and community interviews from the United States, Vietnam, and South Africa that show the perception that it is "dirty", associated with "bad" people, causing shame, embarrassment, and commanding less respect for those affected.[256, 257, 258] There is the fear of isolation and segregation, accentuated in the HIV and MDR epidemics, which also impact on the recruitment of health workers.[248] Stigma creates difficulties for patients in presenting for medical attention and in adhering to treatment.

In rural South Africa, people diagnosed with tuberculosis stopped attending the health

service, even though they had previously been regular attenders.[259] A community-based survey in urban Cape Town identified that people were not keen to associate with patients with tuberculosis.[260] Reduced marriage prospects and risks of divorce, especially for females are issues in Pakistan[261] and Cambodia.[262]

Rejection by families and communities is a major problem in many communities, and impacts on adherence.[263] The stigma is less within families of patients than extra-familial.[263, 264] Those with the disease in Bombay were more likely to seek treatment outside their communities, which resulted in problems with treatment adherence, and with accurate incidence measures.[265] Focus group interviews in the Philippines on former patients found that there was a reluctance to discuss the disease, referred to as "weak lungs", and that open questions were less threatening and more useful in determining attitudes.[264]

8.2.2 Cause/predisposing factors:

Patients' stated beliefs about the causes of tuberculosis also vary in different communities. Many think in terms of predisposing factors, rather than causative agents. It is commonly attributed to drinking alcohol, smoking, poor nutrition, difficult work situations and overcrowding, which beliefs appear to reflect the habits and living conditions of those at risk of the disease.[260, 264, 266, 267, 268] Witchcraft was not a commonly stated cause in studies in South Africa,[267] nor in Kenya,[269] but Barnhoorn reported that Indian patients who did not adhere to treatment were more likely to ascribe their disease to witchcraft than those who did adhere.[270] "Germs" were not often given as a cause in reported studies.[264, 268, 270] Ethnic differences have been described as fundamental to different experiences of disease,[256] but Farmer did not find etiological beliefs to predict adherence.[271]

8.2.3 Patients' knowledge about their disease:

Patients in many studies have described good knowledge of the symptoms of tuberculosis,[256, 260, 263, 264, 266, 267] but in these studies the levels were not compared with adherence. Basic knowledge of symptoms and of treatment was deficient in a study of 42 patients on treatment in Cape Town, none of whom suspected that they had the disease.[272] Other researchers have noted the lack of information given to patients.[269, 273] Knowledge about symptoms and treatment was significantly greater in 52 Indian patients completing treatment compared with 50 who interrupted.[270] Good understanding had a similar effect on adherence in 352 patients in Canada,[251] while poor knowledge had a negative effect on treatment adherence in patients with chronic diseases (not tuberculosis) in an urban area of South Africa.[274]

A randomised controlled trial of intensive education of 205 patients, together with financial incentives, did improve adherence to preventive treatment for tuberculosis, but did not significantly improve adherence of cases of disease.[275] The education package was part of increased attention to patients, and was given together with a financial incentive. Thus knowledge gained may not have been the critical factor in improving adherence. Cuneo's review of factors that improve adherence included patient education which was described as cost effective.[276] Farmer is unconvinced that any educational interventions have influenced the rates of tuberculosis adherence.[271]

8.3 Socio-cultural factors

There are limitations in interpreting statements and answers made at interviews, as expressed by a medical anthropologist.[269] "Socio-cultural attitudes are complex functions which trace back to the early bio-social history of a people. Consequently questionnaires

cannot delve into the subconsciousness which is the presumed base of many human attitudes". Findings about beliefs and cultures relating to illness are often specific to local communities, and may do no more than provide local information.[264] The studies reviewed do however draw attention to some common perceptions, and to the need for local understanding.

When asked the reasons for non-adherence to treatment, socio-cultural reasons ranked high in the list of 59 randomly selected tuberculosis patients in Kenya. They professed a high regard for herbal and traditional medicines, and had a fatalistic approach.[269] Another paper from Kenya reported on focus group discussion findings that traditional treatment is considered a valid alternative to modern treatment. Medical "shopping" causes delays in diagnosing and treating. However "health education will only be effective if health care providers understand the cultural barriers to TB control and if they create the necessary supportive environment".[277] In the South African situation, traditional healers are commonly consulted by patients. The lack of understanding of the social and cultural need for this behaviour is related by Ngubane, with the comment that patients are often reprimanded for attending African healers instead of going straight to western practitioners. The result is that patients are reticent to describe their experiences at traditional healers, and may be deterred from future attendance at a clinic or hospital.[278] Nagpaul, reporting a study of a large number of Indian patients, suggests that the higher attendance rates in employed people and housewives probably reflects a "social preference" for those members of the community who are measured to be of socio-economic value. The study reports on presentation, rather than adherence patterns.[209]

The sensitivity to cultural factors in tuberculosis services is an important trend, recognising the need to understand local beliefs and practices. These range from fears about the social

implications of the disease to cultural activities preventing patients taking treatment.[249] Other reviews have reported on cultural factors being important.[247, 248, 279] Farmer, noting that 85% of patients in Haiti believed that sorcery was a cause of their disease, found no association between adherence and cultural beliefs, and is sceptical about the influence of patient culture on treatment outcomes, suggesting that "economic realities and the quality of programs may override the influence". Whereas health workers give social and cultural explanations for non-adherence, patients have stressed the structural barriers.[271]

Structural barriers to adherence:

Several authors have cautioned that the cultural and psychological interpretation of behaviours must be balanced by an understanding of, and intervention against the many structural barriers to health care experienced by tuberculosis patients.[211, 249, 271, 280, 281] Barriers include socio-economic issues and problems relating to treatment and to health services. It is said that "....the degree to which patients are able to comply is significantly limited by forces quite beyond their control".[271]

Papers describing some of the barriers are reviewed below.

8.4 Socio-economic issues

Patients themselves have described poverty and distance from health facilities as constraints for adherence.[257, 268, 269, 272, 282] Poverty, as measured by income levels, economic needs or social class, was shown to be significantly associated with non-adherence in three case control studies.[270, 283, 284] Studies which cite poor socio-economic circumstances as predictors of poor adherence, are not always able to define the variable responsible.[249]

8.5 Social support and community involvement

Patients who have social support from families and communities are more likely to be adherent.[270, 275, 285, 286] The need to involve local communities in the health care system was emphasised in studies from Bombay,[265] and Cape Town,[287] where involvement and support resulted in considerable success in the control programmes.

8.6 Health service responsibilities

Chaulet and Rouillon are strong proponents of the view that adherence is essentially the responsibility of the health services, and that it is "... nothing more or less than the outcome of a process involving a long chain of responsibilities, extending from the decision makers at the Health Ministry to the treating physicians". If central, regional and district levels of health services fulfilled their respective roles in policy making, organisation, supervision, control, evaluation, and in organising clinics to suit patients' needs, adherence would be good.[211, 246]

The need for a patient-centred approach by health services is endorsed by Sbarbaro who says " ... why should a patient whom we are insisting receive treatment be forced to endure inconveniences, delays, and even discourtesies, that we would not tolerate for ourselves or our families".[280]

8.6.1 Patient-health worker interactions

Many reviews have described that good understanding relationships between patients and carers are important,[249, 253, 280, 286] as well as the need for understanding local health beliefs and cultures.

An intervention study in which tuberculosis clinics were organised to give special attention to patients demonstrated an adherence rate of 100% compared with the rate of 31% in

control patients attending general clinics.[288] Several case control studies compared adherent patients with non-adherers and showed that patient-health worker interaction was significantly associated with improved adherence.[270, 274, 289, 290] Two descriptive studies reported that caring and special attention was important in helping patients to complete their courses.[291, 292]

8.6.2 Supervision of staff:

A large intervention study in Japan, involving 1300 patients, compared two groups of patients, one cared for by nursing staff who had intensive supervision, the other by staff who experienced routine instruction and management. Adherence was significantly better in the supervised staff group.[293] A review by Cuneo of a number of adherence studies endorsed this finding.[276]

8.6.3 Patient follow-up:

Prompt follow-up of interrupters was positively related to adherence in two studies which compared adherent and non-adherent patients in Cambodia and Ghana respectively.[283, 294] The same finding was reported from a review of 35 adherence studies.[276]

8.6.4 Health service access:

Long distances from sources of treatment were problems for adherence as reported from Thailand,[290] India, [292] Ghana,[294] Ethiopia,[295] and the Thai-Cambodian border, where the positive impact of accessible convenient services was noted.[296] By contrast, a Cambodian study of 171 attenders and 46 absconders found that distance was not a factor in adherence.[283]

Long waiting times at clinics was associated with poor adherence.[288, 297]

Social and cultural practices of communities can make it difficult to attend health services. Three examples were provided by a study from San Francisco. The Chinese community

could not manage an early morning clinic, while the African-American population and alcoholic tuberculosis patients with social problems avoided a local clinic. All these groups had reasons for their non-attendance which needed analysis and intervention. Physical accessibility does not imply social acceptability.[298]

8.6.5 Other treatment and disease factors:

Treatment-related factors have been shown to be associated with better adherence. These are simple regimens of short-course treatment,[249, 279, 297] and an initial period of hospitalisation.[249] Side effects of drugs were found by some to be associated with problems with adherence.[274, 283] Others, as reviewed by Haynes, disagreed.[297]

HIV-infection was negatively associated with adherence.[154] A review by Mellins et al showed that severe symptoms did not promote adherence.[286] In fact increasing symptoms have been described as resulting in decreasing adherence.[297]

Symptomatic improvement on treatment, [295, 297] other illness,[290, 295] and specifically substance abuse, mental or physical impairments[253] all had a negative association with adherence. Previous interruption was associated with a risk of non-adherence.[284,297]

8.7 Incentives

The use of incentives, financial, material and social, have been described by some as adherence promoters.[253, 276, 299] Others cite no proof of their effectiveness.[249, 275] A systematic review from the United States of 11 randomised trials which measured the effect of cash or money vouchers given to patients on treatment for a variety of different health problems, concluded that 10 did show positive improvements in adherence.[300] A social incentive described to have some effect was a contractual agreement to complete treatment between patient and provider.[249, 276, 280, 296]

8.8 Patient factors

While data on demographic factors are frequently collected, they have not been shown to affect adherence.[249, 286] Nor have educational and personal patient characteristics.[286]

Treatment adherence in summary:

Adherence is a complex phenomenon dependent on many interacting factors, some of which are specific to local areas and groups of people. One cannot but note that the more one reads, including reviews of most eminent workers, the more contradictory evidence accumulates with positive and negative associations documented for the same factors.

It is clear that health workers need to be much more cognisant of culturally determined health beliefs, and of behavioural theories, as these impact on treatment outcomes. However, in the regions of the world where tuberculosis is most common, economic necessities, and adequate and appropriate health service delivery must be the primary focus of intervention.

CHAPTER 9

TUBERCULOSIS IN SOUTH AFRICA

This chapter includes:

The history of tuberculosis in South Africa

The epidemiology

The SA Tuberculosis Control Programme, past and present

Studies of treatment outcomes

The National tuberculosis review of 1996

Recent studies

Evaluation of the new tuberculosis control programme

9.1 The history of tuberculosis in South Africa

Tuberculosis was introduced into the susceptible population of South Africa from Europe. The magnitude of the problem has differed according to people's previous exposure and their living conditions, and has to a large extent been determined by *apartheid* policies.[301, 302, 303, 304] Before the mid-19th Century and the colonialist era, the disease was not a health problem of Africa. Reports of missionary doctors and explorers confirm this, including statements by David Livingstone that he found no tuberculosis in the interior. The disease was unknown in Negro slaves before they were deported from West Africa to America. It arrived in Africa through colonialists, settlers, fortune seekers and missionaries. It entered South Africa through the ports of the Cape (the brother of Vasco da Gama was the first recorded patient in the late 1400s), spread sporadically at first, but more intensively as more and more European settlers arrived. Not only were there settlers who originated from countries where the disease was a major problem, and who were likely to be infected

or to have active disease, but tuberculosis patients actively sought out South Africa for its warm dry climate. Sanatoria were established in the Cape, in and close to towns of the Karoo. Many patients stayed for years in the hope of being cured. There is no doubt that their disease must have spread to local susceptible people.

The next major factor in the spread of the disease was the discovery of gold and diamonds in the Transvaal from 1868. Miners came from England with dormant tuberculosis infections, which became reactivated under the living conditions to which they were subjected. Some came with active disease. Black miners from different parts of Africa, including Malawi, Mozambique and the Eastern Cape (especially the old Transkei) were recruited as labourers on the mines. Their strenuous work, in most cases appalling living conditions and poor nutrition, and their exposure to tuberculosis had disastrous effects. When they developed the disease they lost their jobs. These men, and those returning home on annual leave, spread the disease among their families and contacts. By 1910, several hundred thousand men moved back and forth between the mines and their rural homes.

Various Commissions were appointed to investigate and report on health care. In 1914, such a group specifically studied tuberculosis and its prevention.[305] Infection rates amongst rural people reached very high levels by the late 1920s.[302]

By 1930, more than 60% of the Black population was estimated to be infected. The disease was reported as a major problem in Transkei.[306]

In 1929, Stevenson-Hamilton wrote that tuberculosis and other pulmonary complaints were major causes of premature mortality among black men of the Lowveld. "Phthisis" affected miners long after their return from the gold mines, and "exacted an enormous toll of

life".[307] In the 1940s, the Fagan Commission heard from the Re . HP Junod who worked in Gazaland, Mozambique, that the migratory labour system had a very serious effect on the health of the local people.[302] The rate of active disease (diagnosed radiologically) of Africans living in the Northern and Eastern Transvaal in 1953 was 0.78 percent or 780 per 100 000.[308] The development of the epidemic continued in the 1940s with large scale urbanisation, and migration of numbers of people to the towns in search of work. Overcrowding, malnutrition, alcohol abuse and stress were the rule. The results in terms of tuberculosis were comparable to those of the Industrial Revolution in England in the mid 1800s.

Since the beginning of the tuberculosis epidemic in South Africa, the incidence in the white population group has declined. In the black and coloured groups, the disease has remained at high levels, emphasising the relationship between tuberculosis and socio-economic conditions. With the formalisation of the *apartheid* policy in 1948, conditions of poverty and oppression, poor living standards, inadequate housing, education and health care worsened in the black population.

9.2 The epidemiology

Tuberculosis became a statutory notifiable disease in 1919 when a Public Health Act was enacted. The policies of the government from 1948 caused fragmented and inadequate health services in many rural and periurban areas, and prevented legal entry and stay of black people in cities. Illegal immigration was rampant with people from poverty stricken rural areas where land rights and opportunities for agricultural economies had been removed. All these factors made accurate enumeration of tuberculosis cases and of the

population denominators impossible. The problems with data collection remain in 1998 in the "new South Africa".

9.2.1 Incidence rates:

Figures 1 and 2, on page 79, show the tuberculosis incidence rates for South Africa since 1921 and the race[1] - specific rates since 1970.[309, 310] Case definition has never been accurate nor standardised. In some places cases were diagnosed by clinical and radiological criteria, in others by bacteriology. Notifications form the basis of cases reported by the Department of Health. These differ from the tuberculosis research programme data which shows higher incidence figures for most provinces and for the country as a whole in 1992.[310] The notification rate increased from 1921 until 1968 (when 372 cases per 100 000 population were recorded), then decreased to 162 per 100 000 in 1986, with a further rise to the 89 300 cases reported in 1993, a rate of 204 per 100 000 population. Estimated numbers of cases for 1996 from the Tuberculosis Research Programme of the Medical Research Council were 158 689, with an overall country incidence rate of 362 per 100 000 population.[311] Tuberculosis accounts for over 80% of all communicable disease notifications to the Department of Health. Differences in rates based on racial categorisation (figure 2) shows a dramatic rise in the "Coloured" group (to 671 per 100 000 in 1995). Black, Asian and White group incidence rates in 1995 were 182, 69 and 16 per 100 000 respectively.

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[1]The term *race* has beeen used in the South African context to denote peoples of different groups. While this is no longer an accepted term, the race-specific rates quoted here are of use to identify risk groups from the old *apartheid* era

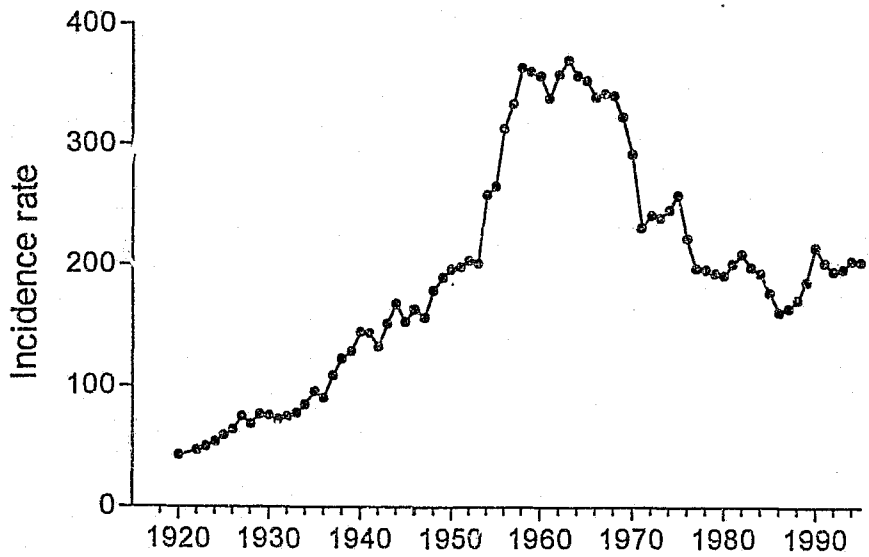


Figure 1: Annual tuberculosis incidence rates in South Africa since 1921

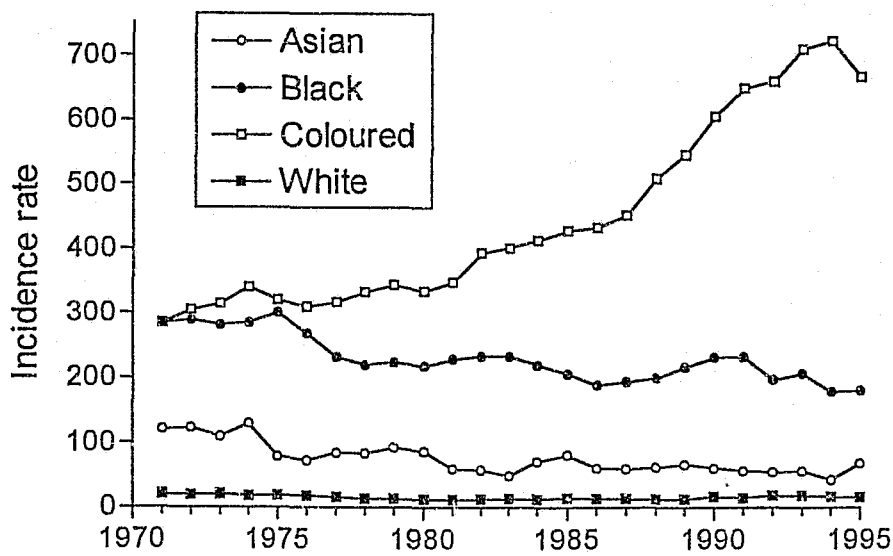


Figure 2: Race-specific tuberculosis incidence rates in South Africa since 1970

Table 2 shows the incidence rates for the 9 provinces of the country, according to notification reports.[312]

TABLE 2: TUBERCULOSIS INCIDENCE IN SOUTH AFRICA BY PROVINCES, 1994

PROVINCE	REPORTED-ALL FORMS	ESTIMATED -SMEAR POSITIVE	PROPORTION OF TOTAL POPULATION
WESTERN CAPE	737	221	0.09
EASTERN CAPE	241	193	0.16
NORTHERN CAPE	442	133	0.02
FREE STATE	513	103	0.07
KWAZULU-NATAL	120	129	0.21
NORTH WEST	112	102	0.08
GAUTENG	164	142	0.17
MPUMALANGA	84	101	0.07
NORTHERN PROVINCE	44	102	0.13
TOTAL	223	140	1.00

9.2.2 Previously treated cases:

Retreatment rates were high as measured from routine data which have reported 8-15% during the early 1990s.[310, 313] Study data reported 30%.[314] This reflects problems with effectiveness of the control programme, despite the availability of internationally recommended drugs.

9.2.3 Mortality data:

Mortality data has long been subject to error in South Africa. Despite the statutory requirement to notify tuberculosis deaths, data is known to be incomplete, especially in the black population. Mortality rates for the City of Cape Town since 1893 are shown in figure 3.[315]

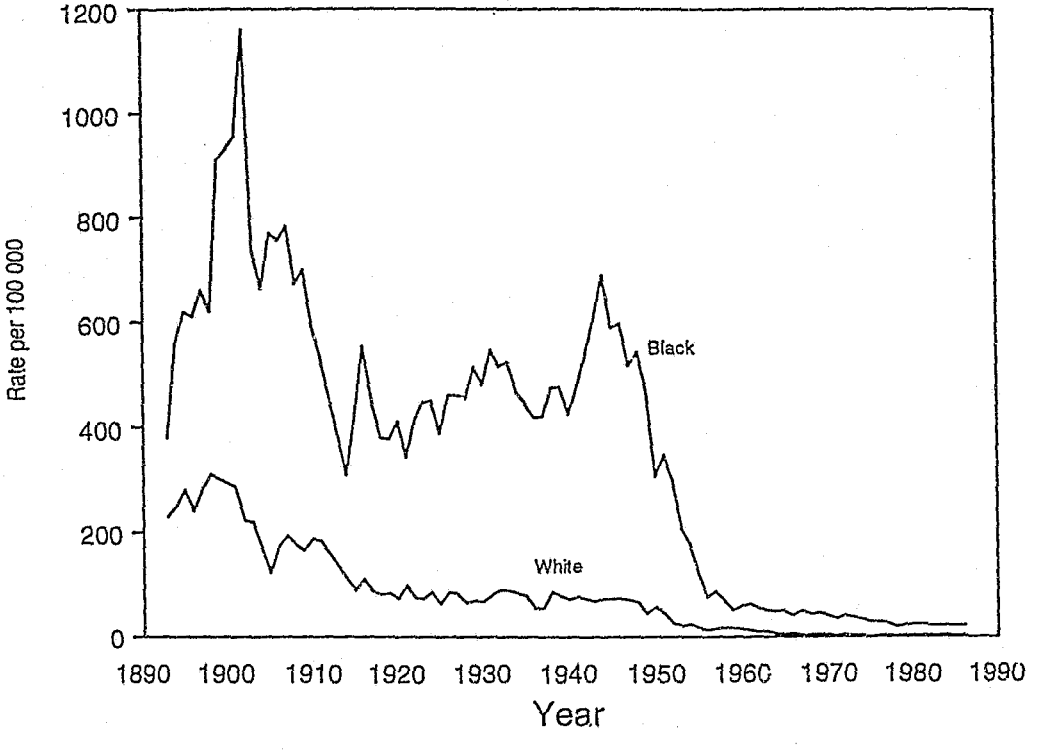
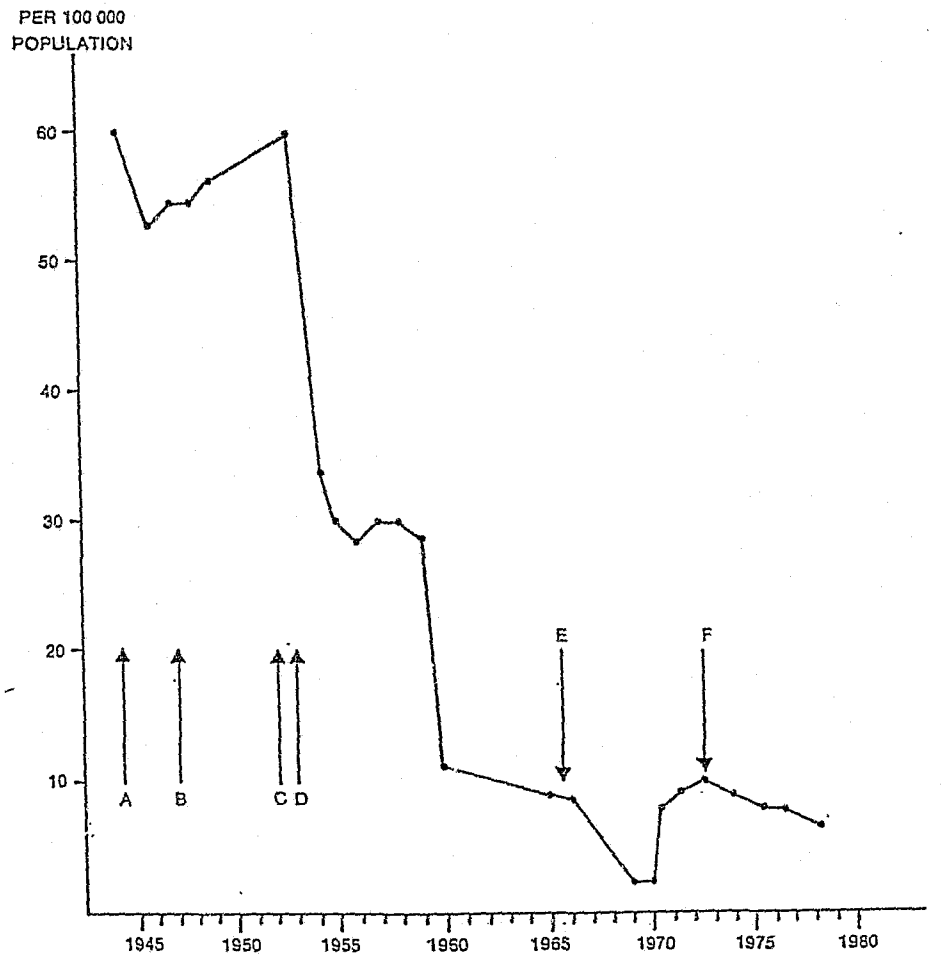


Figure 3: Tuberculosis mortality rates for the City of Cape Town, 1893 to 1986.

Case fatality rates of over 30% were recorded until 1944 when chemotherapy with streptomycin began. The graph of mortality rates in the country since 1944, illustrating the effects of specific interventions, is in figure 4.



A — Introduction of streptomycin, 1944.
B — Introduction of para-amino salicyclic acid, 1947.
C — Introduction of isoniazid, 1952.
D — Intensification of active case-finding, 1953.
E — Compulsory notification of positive PPD-reactors under 5 years of age, 1965.
F — Compulsory BCG-Vaccination of all newborn infants, 1973.

Figure 4: Mortality from tuberculosis in South Africa since 1944

For the black population in rural areas, deaths have only been registered since 1978. For urban blacks this started in 1968. A review of death patterns in 1979 and 1980 demonstrated that a large proportion of deaths (20% on average) have been classified as "ill-defined".[316] There is probably considerable under-reporting of deaths in the population most at risk. Since the early 1960s the mortality rate has been 2-3%.[309, 310] Possible reasons for the low figure compared with other developing countries, where rates of over 30% are reported,[28] are the widespread availability and use in South Africa of anti-tuberculosis drugs which have prevented deaths, and because the denominator of case mortalities has been inflated with cases who did not have tuberculosis. The absence of strict defined diagnostic criteria has resulted in this over-diagnosis.[312]

9.2.4 Prevalence rates:

Bacteriological population-based random sample prevalence rates for rural populations for the period 1972-1978 ranged between 0.8% and 2.5% for microscopically diagnosed cases, and 0.5% and 4.4% for those identified by culture, with rates for the Transkei being the highest. For the period 1979 - 1984, the figures were 0.1%- 1% (microscopy) and 0.4%- 2.4% (culture).[317]

9.2.5 Annual risk of infection:

Tuberculin surveys were carried out in South Africa between 1974 and 1985. Risk of infection estimates ranged between 0.1% and 1.6%.[318] In 1990 the annual risk in 'Coloured' children 5-9 years of age in the Western Cape was 2.5%.[319] The tuberculosis research programme found a rate of 2.3% on the West coast region in 1994.[312]

No further risk of infection studies have been done. It has been recommended that control programmes should be evaluated by annual risk of infection studies.[28]

9.2.6 Tuberculous meningitis (TBM):

The incidence of TBM can be used as an indicator of the stage and severity of an epidemic with more cases with active infection.[320] A constant ratio of pulmonary to meningitis cases can be expected. Styblo suggested a figure of 1 case of TBM per 12 smear positives.[321] The ratio for South Africa overall calculated from notifications over 22 years since 1971 is 1:150. For the coloured population group the ratio for this period was 1:110, and for the black group, 1:120, with considerable variations in the numbers of TBM cases reported between regions, population groups and over time. However a consistency was maintained in the ratio of smear positive to TBM cases.[322]

A study of TBM in the Western Cape showed alarmingly high rates of TBM in young children, 24 per 100 000 children under 5 years of age, which is an index of the extent of tuberculosis disease in that region of high prevalence.[319]

9.2.7 Drug resistance:

Drug resistance has been measured in South Africa since 1965. The prevalence of multi-drug resistance as measured since 1990, is 3% of tuberculosis patients, with 1% primary and 4% secondary resistance. This means about 900 cases per year.[312]

9.3 The South African tuberculosis control programme, past and present

9.3.1 General

In 1979 tuberculosis policy statements included the objectives of reducing the risk of tuberculosis infection to 0.3% and below, and ensuring the treatment of all cases of disease."[323] The cost-effectiveness of the short-course chemotherapy was proved by a local study in 1981 which pleaded for widespread implementation of the regimen.[324]

Until 1995, tuberculosis was essentially managed without a formal control programme (by

international standards), although various manuals, booklets and forms describe the strategies which were health education, supervised therapy, case-finding and BCG vaccination. Guidelines included some, but not all of the internationally recommended programme principles.[325, 326] The failure to prepare and implement a proper programme was to a large extent the result of the political policies of South Africa which were in place until the election of a democratic government in 1994. These policies resulted in isolation of the country with non-participation in the WHO decision-making processes, and in low political commitment to a disease which largely affected the non-white population. In addition, health (and other) services were impossible to plan and implement in the fragmented geographical and political systems enacted through the South African Constitution Act of 1983. These deficiencies are described as the "selective distribution of socioeconomic resources", resulting in a fragmented health service, a weak primary health care system, inadequate central co-ordination of tuberculosis, an insufficient welfare system and lack of community involvement.[327] A keen proponent of tuberculosis control in 1982 admitted that the programme had failed to identify more than 50% of patients, to implement supervised treatment, and to reduce infection and reactivation of disease with consequent high morbidity and mortality. Reasons given were lack of discipline of health workers with no uniform policies for diagnosis and treatment, haphazard, frequently changed control policies, irregular funding, inadequate use of nurses, absence of community involvement and deficiencies of medical infrastructure, notably laboratory services.[328]

9.3.2 Recording cases and treatment outcomes:

Until 1995, the WHO recording and registering system for tuberculosis was not in use in South Africa. The control programme relied on notification as the means of surveillance,

and on additional forms being submitted to the national office. Case load data added new cases to the existing "load", and outcomes were defined as "cured and discharged", "died" and "absconding". The difficulties in establishing accurate numerators and denominators made the data suspect and the programme difficult to evaluate. In 1991, the "cured and discharged" rate was 78%,"died" 5% and "absconders" 17%. The range between the provinces was large - in 1991 the cured rate range was 34% to 102% (the latter was presumably an error of recording in several places at once).[313]

9.3.3 Diagnostic criteria:

Bacteriological diagnosis of patients has not always been achieved, and monitoring during treatment and final investigations has rarely been done.[305, 329] There has been over-emphasis on radiological diagnosis, and excessive use of radiographs.[329, 300] There has been a need for a national policy which includes laboratory facilities for smear microscopy through the country, especially in remote areas, with training of microscopists and on-going quality control.[331]

9.3.4 Programme management:

A number of management deficiencies and needs have been highlighted. A plea was made as long ago as 1982 for a specialised task force to manage the disease and to resolve the problem of the isolation of provincial and academic hospitals from the programme.[332] Particular needs stated by several authors were the implementation of a uniform tuberculosis control programme using standardised means of diagnosis and treatment, with integration of services within a primary care system, and provision of adequate medical infrastructure including laboratory networks.[305, 329, 330, 333]

Large variation in diagnostic and treatment practices was measured within different local health authorities within one region.[329, 330] Failure of the notification system to identify up

to half of infectious cases was described.[333, 334] "Independent" and homeland states were excluded from the data for South Africa.[335] The underlying socio-economic deprivation of communities under the *apartheid* system was described as a predisposing factor and as a major constraint for successful programme implementation.[305, 329, 336]

9.3.5 The Tuberculosis review of 1994:

The South African health department requested Dr Styblo, a world expert on tuberculosis control, previously scientific director of the IUATLD, to review the national programme during 1994. His report reiterated formally what many researchers and health workers had been saying for some years.[337] He found that there was no dedicated tuberculosis control programme, that staff were untrained and unsupervised in their work, that there was no uniform method of diagnosis. If bacteriology was used, there was confusion about the role of microscopy, culture and drug sensitivity testing. Suspects and contacts were often included in the data. The system made it impossible to focus on smear positive patients. Only three drugs (rifampicin, isoniazid and pyrazinamide) were used, and all three drugs were given for 6 months. Administration was daily for some patients, but packs of drug supplies for one, two, four weeks or longer were given to other patients. There was no retreatment regimen in use. The registration systems in clinics were such that no treatment outcomes could be determined.

9.3.6 The World Health Organisation team visits in 1994 and 1995:

A three-person team of experts visited the country twice during 1994 and 1995 to help set up a national tuberculosis register system, to initiate a pilot province project, and to conduct a training workshop. They found that WHO recommended policies and practices were being introduced, and that programme management was being introduced by the advertising of posts at various levels. They reported "guestimates" for national annual

tuberculosis expenditure of 387 million Rands.[338]

9.4 Studies of treatment outcomes

A number of studies have described tuberculosis treatment outcomes in different parts of South Africa since the mid-1970s. These are summarised in table 3 on pages 90, 91 and 92.

Methods differed, but essential features are noted in the last column of the table. The majority of these studies were not able to measure treatment outcome, since the South African programme used no system of registration or recording of outcomes. One column of the table provides references to each study.

The report of the Kangwane tuberculosis programme described the need to identify "simpler, cheaper" methods than "standard data collection" which merely reflect the basic inaccuracies of the system of data collection that was used in South Africa until 1995.[339] This was challenged with the statement that there is no excuse not to have routine information in National Tuberculosis Programmes today, and the recommendation that the established IUATLD information system be used.[340]

Attendance was used as a proxy for outcome in all studies quoted except four- those from three hospitals - Charles Johnson, Emmaus, and Hlabisa, and from the study on the Kangwane "homeland", and was defined as either 75% or 80% or more of possible visits to health services to collect treatment. None of the studies validated the actual treatment adherence, and no cure rates were reported as the programmes did not include sputum monitoring at the end of treatment. The proportion of patients attending well or

completing treatment was very low in most of the studies.

Good attendance/completion:

Five studies reported attendance/completion rates over 80%. Four were in rural areas, Mseleni and Emmaus in KwaZulu Natal, Hewu in Ciskei, Tintswalo in what was the Eastern Transvaal, and one was from a questionnaire study of 68 urban local authorities in the Western Cape. DOTS was used in all but one of the successful areas. The Hlabisa study reported that if patients transferred out are excluded, the proportion completing treatment rises to 83%.

National surveillance figures reported a range of completed treatment rates between 74% and 79% for the years 1985 to 1991.[313] As discussed, these figures are subject to inaccuracies as both numerator and denominator figures were suspect.

Problems:

Some researchers specifically noted problems, which could be broadly classified as health service related or socio-economic in nature. Health service issues were lack of policy on tuberculosis management and fragmented health services (Tintswalo), inadequate resources (Tintswalo and Mseleni), long distances to be travelled by patients to reach services (Moroka, Tintswalo, Estcourt rural areas), inadequate numbers of trained staff (Mseleni and Estcourt), communication and transport facilities within the health service (Estcourt), poor hospital referrals (DiepMeadow, Soweto), and poor compliance of doctors with recommended policies (Moroka). The social and economic constraints noted were poverty, cultural beliefs, and the high mobility of people.

TABLE 3: TREATMENT OUTCOMES FROM SOUTH AFRICAN STUDIES

PLACE	REF	PERIOD	NO. OF Pts	OUTCOMES (%) *				FEATURES
				COMPL	INTER	DIE	TF	
Kalafong hospital, Pretoria	334	1975-85	100	22	13		54 hosp	44 patients referred for community-based treatment. 50% of those completed.
Transkei - District hospital (St. Lucy's)	341	1976	90	M 42 F 32 Ch 25				Attendance measure over 7 months One third of hosp. deaths due to TB Attendance not related to distance from hosp. Recommend decentralisation to clinics
KwaZulu - District hospital (Ch J)	342	1977-79	87	62	25			DOTS, Intermittent twice a week for 9 months Outcome Recommend decentralisation to clinics
Soweto - Local clinics	343	1978	560	28	72			80%+ Attendance measured Treatment 12 months, no rifampicin Age under 30 years predicted attendance, not sex, nor clinic Recommend decentralisation to clinics
Boputhutswana - District hospital (Moroka)	344	1978	95					Treatment 18-24 months + ethionamide 6 months High proportion 21-40 years of age 36% retreatment High relapse rate Problems: dr compliance, distance of patients from clinic, cultural beliefs
Gazankulu - District hospital (Tintswalo)	345	to 1980 1983 +	111 279	39 86				Treatment 4 months in hospital, 2 months out-patient treatment 80%+ attendance measured. DOTS from 1983. Constraints: poverty, unemployment, fragmented "homelands", distances, no TB policy, health service resource inadequacies (staff, transport, drugs)

* outcome key: COMPL= completed, INTER= interrupted, DIE= died, TF= transferred

TABLE 3 continued: TREATMENT OUTCOMES FROM SOUTH AFRICAN STUDIES

PLACE	REF	PERIOD	NO. OF PTS	OUTCOMES (%) *				FEATURES
				COMPL	INTER	DIE	TF	
KwaZulu - District hospital (Mseleni)	346	1981-86	270	85	4	1	3	Treatment HRZE* twice weekly. No DOTS 90%+ Attendance measured. Constraints: inadequate no. of staff, vehicles for follow-up.
Ciskei - One district (Hewu)	347	1983-84	175	86 (incl 11% in hosp.)	14		3	80%+ attendance measured. Treatment decentralised to clinics, 6RHZS/E*. DOTS at clinic or by Village Health Worker.
Natal Escourt - town + rural	348	1985	50	All 48 Town 68 Rural 28				80%+ attendance measured. Sample selected for clinic treatment. Treatment short-course. Constraints to care in rural clinics: Staff training and support, poor communication and co-ordination, distances, transport.
SA overall E Cape W Cape N Tvl SA overall SA overall	349 349 313	1985 1986 1991	55500 56500 86714	78 68 85 79 77 79	16 25 11 16 17 17	6 7 14 5 6 4		National surveillance figures covering health regions, excluding "homelands". Best & worst regions selected for table. No outcome data. Definitions: cure= completed regimen, defaulter= not attended for 2 months. About 10% said to be retreatment.
Free State - All clinics	350	1986-88		61	36	3		Black patients only

* H = Isoniazid, R = Rifampicin, Z = Pyrazinamide, E = Ethambutol, S = Streptomycin

TABLE 3 continued: TREATMENT OUTCOMES FROM SOUTH AFRICAN STUDIES

PLACE	REF	PERIOD	NO. OF I TS.	OUTCOMES (%) *				FEATURES
				COMPL	INTER	DIE	TF	
W Cape - 68 local authorities	351	1984	4400	83				75%+ attendance measured. Treatment short-course. DOTS. Lowest "compliance" rates: age <5 years, teenagers, blacks, unemployed.
Natal -District hosp. (Emmaus) Natal clinics	352	1987-89	536	92 64	5	3		Outcomes measured. DOTS with community supporters, mainly trained village health workers. Main reason for interruption: "patient moved/unknown".
Kangwane -all 3 regions	339	1990	751	46	26	8	20	Outcome measures, but not routinely collected.
DiepMeadow (Soweto)	353	1991	420	14	43	4	39	80%+ attendance measured. Treatment 6RHZ, no DOTS Poor hospital referral process. Recommend recording system.
KwaZulu -District hosp. (Hlabisa)	354	<1991 1991-92	903	18 74	9	7	10	Treatment 6RHZE twice weekly DOTS with community supporters
Western Cape -One clinic (Elsies River)	355	1992	257	68	32			75%+ attendance measured. DOTS (comparing clinic, volunteers and crèches)

9.5 The National tuberculosis review of 1996

The next major event in tuberculosis control in South Africa was a national review of all 9 provinces and the national office by a team of local and international experts in June 1996. Representatives of the WHO reported on the event.[356] The review acknowledged the transition period in which the public sector of the country was operating at the time of the review, but stated the enormous burden imposed by tuberculosis, which has an annual incidence rate of 311 per 100 000 population, one of the highest in the world, despite an annual expenditure of R500 million on tuberculosis control activities. The incidence rate, together with the emergence of multi-drug resistance and the growing HIV epidemic, was said to have created one of the most serious tuberculosis crises in the world.

Many strengths were recognised and included excellent resources of all kinds at government and non-government levels, acceptance of the DOTS policy in national guidelines, a functioning pilot province, regular drug supplies, and international cooperation.

However there were serious weakness in the failure of all government levels to respond to the crisis, inadequate management systems for resources, finances and information, incomplete implementation of DOTS resulting in inadequately treated patients, absence of an appropriate microscopy service, and inadequate use of the new registering system. None of these weakness were new, most had been commented on in the past.

9.6 Recent studies

Problems are still being reported. A study from a rural area found deficient case registration, non-use of microscopy for diagnosis, absent laboratory quality control, inadequate transport resources for community services and inadequate drug supplies.[357] A researcher working in an area of high incidence of tuberculosis has suggested alternative approaches to cope with the

increasing load of patients in the use of intermittent therapy with DOTS for the full duration of treatment, and initial smear diagnosis with no further bacteriological monitoring.[358] Problems relating to the monitoring, especially in rural areas have been documented.[329, 332]

9.7 Evaluation of the new tuberculosis control programme

The new register has made it possible to measure bacteriological coverage. The National Tuberculosis Control Programme has reported on case finding and treatment outcomes for two years of the new programme, 1995 and 1996. Case reporting rates for the whole country (reported cases as a percentage of those expected) for the 2 years were 46% and 60% respectively, with large variations between provinces. Bacteriological coverage rose from 75% in 1995 to 82% in 1996. Completed treatment outcomes for new smear positive cases were 72% and 73% for the 2 years respectively, including only a 50% cure rate, and an interruption rate for both years of 18%. The range of successful outcome rates for 1996 between the 9 provinces was 58% for the Northern Cape, a province with the lowest reporting rate of 9%, to 83% in Mpumalanga, the country's pilot province, where the reporting rate in 1996 was 51% and 46% for the first two quarters of 1997.[359] Assessment of the control programme remains difficult because of poor reporting rates.

Tuberculosis notifications for 1996 totalled 65 300. However the TB register total was 36% more at 102 000. The largest discrepancies were for four provinces, Eastern Cape, KwaZulu Natal, North West and Northern Province, in all of which the register figures were significantly higher.[360]

CHAPTER 10

THE DISTRICT HEALTH SYSTEM AND INTEGRATION OF TUBERCULOSIS SERVICES

This chapter includes:

Definitions

Integration of tuberculosis services within the district health system

The development of the district health system in South Africa

10.1 Definitions

The District health system and primary health care:

It has been recognised since the landmark meeting in Alma Ata in 1978, that fundamental health care provision is at primary level, with emphasis on essential health care delivered through intersectoral action and community participation, based on the principle of equity.[361] The focus changed from provision of medical services, to a community-oriented approach, with service delivery appropriate to needs, accessible to people, and more rational for service providers, in that peripheral services are able to cater for a large percentage of needs. Such health care is "acceptable only if it is both an integral part of the community it services and intimately linked with the next tier of services above it".[362]

Ten years after the primary health care declaration emanating from the Alma Ata Conference, a number of meetings and documents proposed the district health system as the recommended structural basis for the delivery of comprehensive health services.[363]

A district is the most peripheral unit of local government serving a population of between 50 000 and 500 000, within which collaboration with other functional units can most easily

occur. **The district health system,** as a self-contained part of a national health system, delivers all the components of primary health care through a process of decentralisation, integration and coordination. It allows bottom-up and top-down planning, integrating the needs of communities and of health managers, in the delivery of care at the lowest service point.

Crucial to efficient and effective functioning are a number of activities. The first is **good management** which involves setting objectives and targets, particularly for decentralised systems, creating a district health team, defining the roles of hospital and community-based primary care services and establishing referral systems between each of these, and managing important transport and equipment resources. Other activities are **financial and resource allocation, intersectoral action, and community involvement.** This latter can range from developing a revolving fund for the purchase of drugs (the example from Mali), to management of clinics and health centres by community committees (as reported from the Kasongo project, Zaire).[364] Finally, **human resource management** requires supportive supervision, in-service training at district level, clear job descriptions and the absence of disincentives. Frequently overlooked problems of staff are late payment of salaries, poor working and living conditions, and missed opportunities for job promotion by those sent to remote areas. Known demotivating factors are isolation, fear of making mistakes which affect people's lives, having to work without proper supplies, boredom and routine, and conflicting work pressures (as in the need to satisfy community members and health managers).[365]

The desired output of a district system is a structure which accommodates comprehensive and integrated primary health care services. Implicit in such services are hospital services geared to support the primary care network, and effective referral systems between the district clinics

and hospitals. The district hospital has an important role in being the referral point for sick people who cannot be managed at clinic level. However the challenge is to direct appropriate resources, training and recognition to the clinic level. It is suggested that district centres should not reside within hospitals, but should be provided for and supported from provincial levels.[362] Hospitals may fragment the continuum of care in that when patients are discharged there may be little continuity, as hospitals do not see themselves responsible for follow-up.[366]

Integrated and vertical health programmes:

Until the 1970s, many health problems were addressed through vertical programmes which focused on particular problems, using specific resources. Examples were tuberculosis, malaria, and smallpox. Although they seemed to produce quick results, these may well have resulted from overall development of the infrastructures, rather than from specific interventions. In addition, these parallel efforts duplicated resources, and were fragmented at the points of delivery to communities. The move to integration has been an attempt to make services comprehensive, coordinated and "user-friendly". The approach relies on team work, good leadership and pooled financial resources. Problems often encountered in the change are salary disparities of staff of previous separate programmes, and resistance to integration of services by health workers.[367] Since integration is frequently perceived as increasing the responsibilities and work load of clinic staff, this issue has to be addressed by training, support, and motivation of staff to deliver patient-oriented care.

A population with many health care needs is thus served at district level by integrated primary care functions, which have specialist support at regional and national levels.[368]

10.2 The integration of tuberculosis services within the district health system

Several reports have emphasised the need for an integrated approach for tuberculosis services, and have expanded on the functions of a tuberculosis control programme at primary care level. A network of accessible treatment centres should provide case finding facilities (direct sputum examination for suspected cases), treatment with standardised drug regimens, monitoring of patient adherence to treatment, maintenance of patient records, and referrals for specialised advice as necessary. The control programme must be guided and supported at the next health care level.[368, 369, 370, 371, 372, 373] A report from Turkey suggests that a separate system for tuberculosis care is stigmatising for patients, as well as being less efficent.[372] Specific guidelines from WHO recommend tuberculosis control as an integral part of primary health care.[374] Nagpaul and colleagues researched patients in India, and found that with increasing distance (beyond 6.3 kilometers) from a specialised tuberculosis clinic, fewer patients attended. There was no reason to believe that the disease was less common at greater distances, in either urban or rural environments. The report concludes that local, accessible clinics should diagnose and treat patients, and that specialised centres should have a managerial role in maintaining standards, evaluating, and acting as referral centres.[209]

Good tuberculosis services are dependant on a functioning district health infrastructure. Needs are for efficient diagnosis at clinic level, with all that that entails in terms of sending sputa specimens to district hospital laboratories, and receiving timeous results, and for ensuring that diagnosed patients complete treatment courses. Diagnosis is best done at local clinics, which are accessible and acceptable to patients, in order to reduce delays caused by problems reaching hospitals. Treatment follow-up is best done by health workers familiar with the social and physical constraints of patients, and who act as soon as non-adherence is recognised. All these aspects are best integrated within the functions of a clinic service within

the organisation of a district health system.

Many tuberculosis services have run as vertical programmes, with different teams of staff responsible for organising supporters, monitoring adherence and delivering drug supplies. These are very resource intensive, and often too centralised to identify and solve patient problems at community levels. Tuberculosis outreach work is difficult because of the perceptions that community-based programmes are outside the role of clinics, the lack of time for workers to leave busy clinics, and lack of clinic-based transport. In some countries, health workers use various forms of clinic-based transport, including bicycles, motor-bikes, or horses. In Guatemala, a system of health worker responsibility for a defined geographic section of the community, with dedicated time (two days a week) to visit the entire area, ensures that the health workers are in touch with local health needs, that specific problems are identified.[367]

10.3 The development of the district health system in South Africa

South Africa emerged in the early 1990s through decades of non-democratic rule, isolated from major thinking and developments in equitable health care delivery. Confounding the absence of district systems was the fragmentation caused by the *apartheid* policy, which had carved the country up into multiple separate "homelands", without geographic or administrative logic. Pleas to introduce the district system emphasised that "the only feasible approach to our health problems is well managed, comprehensive PHC based on a DHS".[375] In 1994, the new government committed itself to the primary health care approach, and to the development of the district system.[376] By the end of 1996, 157 health districts had been demarcated, and more planned. The district development has been slow, since it is inextricably bound to local government formulations, which involved newly appointed bodies and district health authorities. Problems have included merging salary scales and conditions

of service of staff from previous separate programmes, changing centralised, top-down management structures, involving communities, and health worker uncertainty and resistance to change. [377, 378]

The Health Systems Trust is a non-government organisation that has been in the forefront of informing about and motivating for the district system, and in setting up sub-district initiatives.[379] There is a clear need for a national focus on health centre development, as supported by the WHO's Division of Strengthening of Health services,[350] and as was recommended by South Africa's own "Gluckman Commission" in the 1940s.[381] Tollman et al have cautioned against the linear process of reform which proceeds sequentially from national to provincial to local levels, and can delay progress at each level.[382] Initiatives at local levels will pave the way for national models, and deserve support.

The District System in the Bushbuckridge sub-region of the Northern Province:

During the period 1990 to 1994, the concept and implementation of a district system for the area began to emerge. This was facilitated generally by the focus on the district system concept, including the issues of decentralisation of health services. More specifically, it was clear that the complex boundaries set up in the "apartheid" era needed to be unravelled. In 1992, the local district interim committee set up a demonstration rural district health system.[383] A health sub-district was established with an epicentre at Agincourt health centre (under Tintswalo hospital), under the direction and support of the Health Systems Development Unit of the Department of Community Health of the University of the Witwatersrand. The initial phase included identifying health needs, defining and establishing community involvement and a clinic referral system to the health centre, which had a small laboratory. Constraints to further development were the lack of logistical support, and the fact that management

remained in the hands of the district hospital. The most recent period, 1996/97 has seen the establishment of Bushbuckridge as a sub-region of the Northern Province, with a degree of authority over staffing and budgets. This is in the nature of a compromise to quell the heated arguments about the provincial siting of the area. Political factors appear to influence the province in which this area is sited. These have certainly retarded progress to a functioning district system.

In summary:

Tuberculosis services should be integrated within district health services as part of the responsibilities of all health workers at peripheral levels. However, because of the specific public health implications of non-adherence, and the lack of resources for follow-up in many remote rural areas, where villages and population are widely dispersed, support from the district community services is often necessary. This is usually a team with responsibility for at least some other community health services, all or some of communicable disease monitoring and control, the immunisation programme, maternal and child health, or mental health.

SECTION 2

THE INITIAL STUDY OF TUBERCULOSIS IN THE TINTSWALO DISTRICT

This section introduces the study area and its population, and describes the record review of patients with tuberculosis for the period 1992 to mid-1994. The following chapters are included:

11. The background to the study: the Tintswalo district and its population
12. Tuberculosis policies and practices at Tintswalo hospital during 1992 and 1993
13. A record review of patients with tuberculosis admitted to Tintswalo hospital in the period January 1992 to June 1994

CHAPTER 11

THE BACKGROUND TO THE STUDY: THE TINTSWALO DISTRICT AND ITS POPULATION

This chapter includes:

The history, geography and political systems of the study area

Health services

Setting up the tuberculosis research project

11.1 The history, geography, and political systems of the study area

The Tintswalo district is situated in the Bushbuckridge area, a subregion of the Lowveld region of the Northern Province of South Africa. Figure 5 on page 104, is a map which shows the position of Bushbuckridge in the Northern Province of **South Africa.** Figure 6 on the same page shows the **Gazankulu and Lebowa homelands** with the **Mhala and Mapulaneng health wards** as they were before 1994. These wards covered areas of 1250 and 800 square kilometres respectively. Bushbuckridge is bordered on the West by the northern part of the Drakensberg mountains, on the East the Kruger National Park, on the North by the Orpen road, and the South the Mpumalanga provincial boundary. The three hospitals of the newly demarcated districts, and the clinics are included in this map.

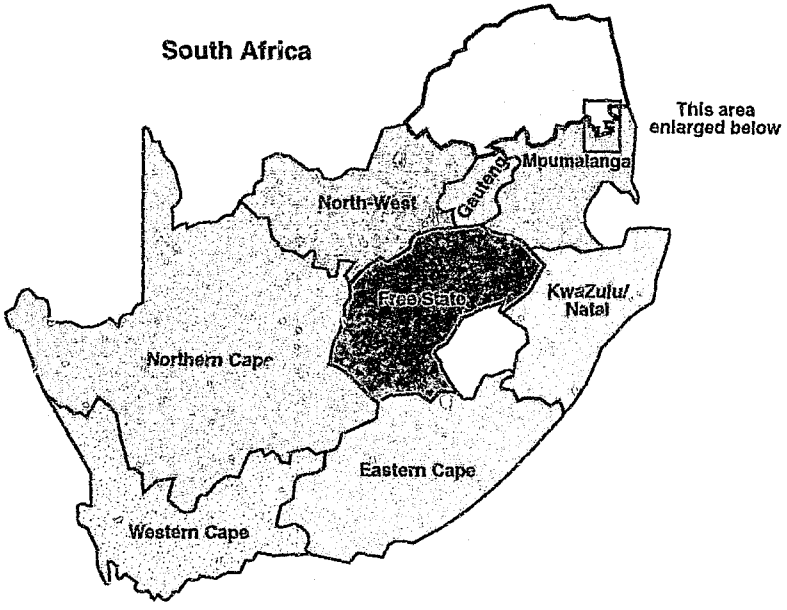


Figure 5: The position of Bushbuckridge in the South East of the Northern Province

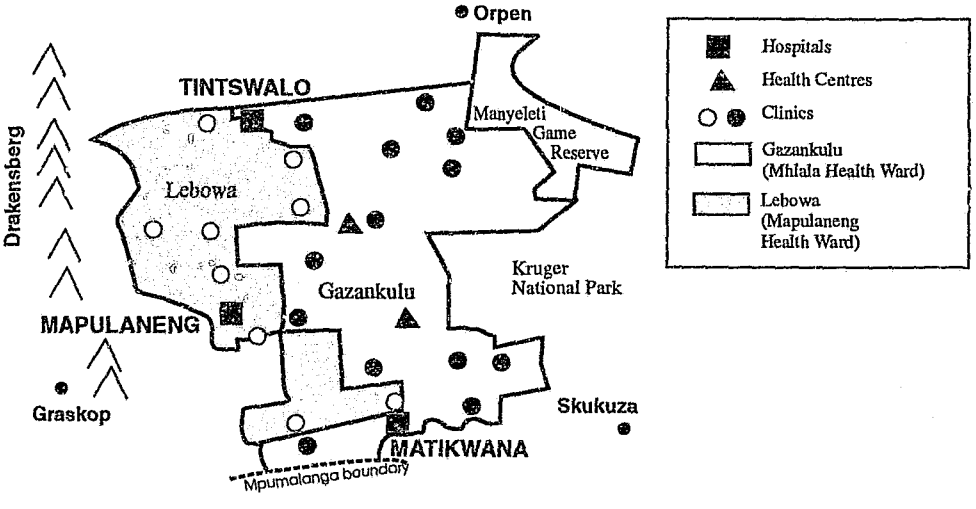


Figure 6: The study area in 1993 showing the "homelands" of Gazankulu and Lebowa with health facilities

The soil of the low lying area was always poor, neither fit for human habitation, nor agriculture, but most appropriate for game farming. One sixth of the Lowveld was suitable for settlement, and taken up by white settlers in the mid-1800s.[307] Tropical fruits are grown, but water supplies are the limiting factor. The climate is intensely hot and humid, summer temperatures reaching over 40 degrees Centigrade. There are forestry plantations against the mountains where rainfall is higher. These contain exotic trees which drain the underground and stream water, so that in the dry season of the year, the flow of the previously perennial local Sand river, a tributary of the Sabie, ceases.

The population is mainly people of the Tsonga (also spelled Thonga) and Northern Sotho groups. Tsonga people originated from the Nguni tribes who fled from Shaka's Zulu armies, and migrated northwards in the 1820s and 1830s. A band under the leadership of Soshangane settled among the Tsonga people of Mozambique, carving out an empire known as the Gaza. Some ascribe the name to an ancestor of Soshangane, others to the meaning which is blood, recalling the violent fighting that took place. The Tsonga were ruled by the Royal house of Gaza until it succumbed to the Portuguese in 1895, and were called Shangaans after their founder. With the collapse of the empire, many fled west into what became known as the southern Lowveld.[384]

Apartheid legislation established "homelands" during the period 1960 to 1985. Two such homelands were Gazankulu, mainly in the Lowveld, and Lebowa, which consisted of patches of land across the north and eastern parts of the Transvaal. Numbers of people were moved into the Lowveld as part of the Nationalist government's grand plan to segregate people on an ethnic basis.

Population size estimates for the early 1990s for the Mhala area (part of Gazankulu) were 230

000, including 30 000 refugees from Mozambique, and for 200 000 Mapulaneng (part of Lebowa). An additional 70 000 people living on farms brought the total population for Bushbuckridge to some 500 000.[385] The Lebowa areas were largely populated by Sotho-speaking people, those of Gazankulu by Shangaans.

Since the new South African government took office in 1994, homelands have been incorporated into the nine newly demarcated provinces. A dispute has raged in recent years concerning the provincial boundary line around Bushbuckridge. It is defined in the Constitution Act of 1994 as part of the Northern Province. The community-favoured option is for the area be placed within Mpumalanga province. No final decision has been reached. The uncertainty and unhappiness around the issue has impacted on the allocation of health resources to this region, on the social security of staff and on the establishment of proper management systems.

People in this area are among the poorest in South Africa. Table 4 on page 107 gives the mean household and per capita incomes for different groups in the country for 1994, according to data from national and provincial samples.[386]

The black population of the Northern Province had the lowest monthly incomes in the country. Sixty eight percent of the Northern Province black population were found to be in the two lowest quintiles (poorest 40%) of the country.

TABLE 4: MEAN MONTHLY HOUSEHOLD AND PER CAPITA INCOMES FOR DIFFERENT GROUPS IN SOUTH AFRICA, 1993/4 [386]

	Monthly Household income (Rands)	Monthly Per Capita Income (Rands)
Whites in Gauteng	6653	2240
Metropolitan areas	3517	1254
South Africa overall	2089	710
Black rural	819	250
Black Northern Province	723	135

Main sources of income were found to be regular wages (53%), these being from migrant labour, pensions and grants (20%), remittances (11%). Self-employment (5%), agriculture (4%), rents (4%) and casual labour (3%) made up the rest. Unemployment rates in 1994, according to the SALDRU (South African Labour and Development Research Unit) report, were 53% among the poorest quintile, where rural Northern Province blacks are placed. A household survey of 723 people in the Mhala-Mapulaneng area during 1993 confirmed the high poverty level. The mean monthly household income was R520, the median R300 and the mode R200, which figures emphasize the desperate poverty of the area. There were a mean of 7.5 people per household. Forty seven percent of the population in working age categories were unemployed.[387] Given the overcrowding and the inhospitable geography, subsistence farming adds little to household incomes.

Costs of health care, distance, and availability and cost of transport were the major barriers to health care for Africans, as reported from the first national household survey in South Africa in 1994.[388]

Malaria, other tropical diseases and health problems of developing communities are

common in Bushbuckridge. They include diarrhoeal diseases of children, malnutrition, respiratory infections, typhoid fever, skin diseases, tuberculosis, sexually transmitted diseases and domestic accidents including paraffin poisoning. Other problems reflect periods of urbanisation of some of the population. Hypertension and its complications and alcohol and other forms of substance abuse are increasing. Many of the men have spent periods working in mines and have pneumoconioses. (JCA Davies, personal communication) HIV and AIDS are increasing in prevalence.

11.2 Health services of the area

District Hospitals:

Tintswalo hospital (the name means mercy) started as an American mission station/dispensary near the site of the existing hospital in 1930. It was taken over by the Transvaal Provincial Administration in the early 1970s, until the establishment of the Gazankulu homeland, under which authority it was managed until the new South African government abolished the homeland system in 1994. The hospital with some 400 beds, has provided primary and secondary health care for the local communities of the Lebowa and Gazankulu homelands, as well as to people living north of Bushbuckridge in neighbouring areas outside the "homeland". The population served in the latter areas were mainly farm-workers employed on land owned by white farmers. In practice many people living in the Mhala district live closer to Mapulaneng hospital and attended there, while many "Lebowa" villages are closer to Tintswalo hospital. Figure 6 on page 104 shows the position of the hospital and clinics. At the time this present study started in 1993, Tintswalo hospital had responsibility for 16 clinics in the Mhala health ward, all to the south and south east of the hospital, itself sited on the north west corner of Mhala. The

distance to the furthest southernmost clinic was 55 kilometres, while distances to two of the nearer clinics which were within the Lebowa homeland (managed by Mapulaneng hospital) were 8.5 and 6.5 kilometres, Buffelshoek and Brooklyn respectively.

Tuberculosis services:

During 1983, research on tuberculosis revealed that for 1980 and 1981, 42% of patients received "enough" treatment. There were no set policies for diagnosis or treatment, relationships between staff and patients were poor and there was no DOTS. Numerous constraints experienced by communities and health service providers included poverty, unemployment, the fragmented homeland system, absence of community participation, long distances to be travelled for treatment, inadequate transport availability for staff, inadequate drug supplies and staff numbers. The service was reoriented to provide acceptable patient care, DOTS in the community, with policies for diagnosis and treatment. The completed treatment rate for patients admitted to the hospital unit rose to 84% in 1982 and 86% in 1983.[345] No studies had been done since that time, until the present research project.

The issues consequent upon the lack of a district health system in the area have been reviewed in chapter 10. Up until the time the research was completed, despite the abolition of the Lowlands, health authority responsibilities for clinics in the area had not changed. The intention is to demarcate three districts, each to be served by one of the existing hospitals in Bushbuckridge - Tintswalo, Mapulaneng and Matikwane.

11.3 Setting up the present tuberculosis research project

In 1993, health service managers and staff involved with tuberculosis services were asked (by the author) about the process and outcomes of tuberculosis management. Answers on outcomes were not readily available, as there was no means of evaluating services, except by analysing each individual patient record.

Summarised components of the research project:

* *The initial phase of this research started during 1993, and was a description of the policies and practices regarding tuberculosis, and an analysis of admissions to the tuberculosis ward at Tintswalo hospital during a two and a half year period, January 1992 to June 1994.*

  These are reported in section 2 in chapters 12 and 13.

* *The next phase was an intervention study of the effects of different systems of delivering tuberculosis services in the district. This followed the results of the patient record review, and was set up in mid 1994, with the cooperation of the Tintswalo hospital. This part of the study is described in Section 3.*

* *Section 4 is a description of patients and community member interviews which were done during the intervention study.*

CHAPTER 12

TUBERCULOSIS POLICIES AND PRACTICES AT TINTSWALO HOSPITAL DURING 1992 AND 1993

This chapter includes the study of policies and practices at Tintswalo hospital:

Objectives and methods

Results

Conclusions

12.1 The objectives and methods

The study had the following objectives:

i) To identify the staff of Tintswalo hospital and its community services who were involved in tuberculosis management, and to describe their roles

ii) To determine hospital policy for the diagnosis and treatment of patients with tuberculosis, and the extent to which the staff complied with the policy

iii) To determine how non-attending patients were managed

iv) To describe the role of staff in the management of tuberculosis in this health ward

v) To determine to what extent tuberculosis services were integrated within the district clinics

Methods:

Observations and visits:

The methods used to manage patients, both those who were in-patients and those who attended as out-patients, were observed. Community and clinic visits were made with the community

nurse and the health educators. Monthly meetings of the tuberculosis team of the hospital were set up and attended by the research team over the period of the study.

Staff Interviews:

All staff involved in tuberculosis management at Tintswalo hospital were interviewed and asked to describe their roles. Those included were the medical superintendent, the community health specialist (who was responsible for all community services including tuberculosis), the nursing managers of the hospital and of community services, the doctor responsible for the tuberculosis ward, the nurse in charge of the ward, other ward nurses, the tuberculosis community nurse, health educators, pharmacist, laboratory technicians, hospital administrator and other hospital doctors. The interviews were conducted informally to gather information about staff responsibilities and procedures. In addition, staff were encouraged to write out their job descriptions and any constraints under which they worked. There were many discussions with tuberculosis staff to clarify and discuss job descriptions and matters of policy and practice.

Results of this preliminary study of policies and practices were not quantified, but served to provide an indication of activities, and as background for the record review study which followed.

12.2 Results

12.2.1 General:

During 1992 and early 1993, there were no written policy documents in use for tuberculosis management. Patient diagnosis and treatment was the individual practice of successive medical officers responsible for the tuberculosis ward. Senior ward nurses had little role in the

management of the system, being concerned only with individual in-patient care, and the smooth running of the weekly out-patient clinic held in the ward.

The follow-up care in the community was the responsibility of a three-person team composed of a community nurse and two health educators. The job descriptions of the health educators[1] was not written, and their line of authority was a source of confusion and problem. According to the community tuberculosis nurse[2], they were under her jurisdiction; according to the hospital nursing managers, they fell under the community nursing manager[3]. Their activities tended to be somewhat undirected and unsupervised, without clear accountability.

12.2.2 Suspected cases and diagnosis:

Suspected cases of tuberculosis requiring admission because they were too ill for out-patient investigation were referred to a medical ward for confirmation of the diagnosis. Occasionally they were admitted directly to the tuberculosis ward. Out-patients were investigated from the out-patient department.

The use of bacteriology for diagnosis and treatment monitoring was haphazard. Sputum bacteriology was usually used (both tuberculosis microscopy and culture tests) to confirm the diagnosis, chest radiography was done when possible (occasionally inadequate water supplies to the hospital made this impossible). Confirmed cases from the wards or out-patient department were sent to the tuberculosis ward for management. Some out-patients with positive results were not or could not be traced, thus were not treated.

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1 Health educators were responsible for education of patients and for tracing non-attenders. In addition they took patients home on discharge when transport was available.

2 The community tuberculosis nurse was responsible for the management of patients outside the hospital, thus for ensuring that all patients completed their treatment. In fact she often acted as ward sister when that person was on leave, or off duty.

3 The community nursing manager was responsible for all community services, including tuberculosis.

12.2.3 Hospital Management:

Most patients were admitted for between 3 and 6 weeks (the exact duration depending on the clinical condition of the patient). Ward treatment was usually rifampicin, isoniazid and pyrazinamide drugs in separate, non-combined form. For some, ethambutol was added, without any specific policy guidelines. Patients received some education at individual and group levels while in the ward, with contributions from the doctor, ward nurses and health educators. There was no coordination of the education, no visual aids and no evaluation of the educational activities.

Occasional patients had their treatment period extended if they did not appear to be responding clinically. Some were observed to have had periods of up to 12 months' treatment for pulmonary disease. Three or four cases of drug resistance had been encountered by ward staff during the year 1992/93. These patients had been referred to Rietfontein hospital in Johannesburg. Cases of non-pulmonary tuberculosis were uncommon. They were managed in the ward on longer periods of treatment, in consultation with a visiting specialist if available, or were referred to a tertiary hospital.

Children diagnosed with tuberculosis should have been treated and notified in the tuberculosis ward. Few were admitted to the tuberculosis ward. HIV tests were said to be routinely performed, with informed consent.

12.2.4 After discharge:

On discharge, some patients were taken home in a hospital vehicle by the health educators, others made their own way home. There was no defined system for transporting patients to their homes, availability of a vehicle being a determining factor. A vehicle was, on average, available once or twice a week, but through the hospital vehicle pool only, not dedicated to the

tuberculosis programme. Drugs were packaged in supplies for 1,2,3 or more months by ward nurses and patients given a supply to take home, usually enough for one month. They were asked to return in one month to the TB outpatient clinic situated in the TB ward on a specific date. At that visit there was a clinical assessment, further education and encouragement, and a further supply of drugs given, usually for three or two months. Another appointment for the TB outpatient clinic was given. At the second outpatient visit a third appointment was given, usually for the last visit at the end of 6 months of treatment. The drug supply given was again for 2 or 3 months.

There was no documented nor observed directly observed therapy short-course (DOTS) system in operation. There was no bacteriological monitoring during treatment, nor at the end of treatment. There was no system for documenting non-attending patients, nor for their tracing by the community team. Some visits were made to patients who had already completed a course of treatment, and numbers of visits were made to adult contacts of tuberculosis patients. There was no specific policy to trace child contacts of smear positive cases. Outcomes of the visits were recorded on the patient's cards kept in the ward.

12.2.5 Records:

All patient files were kept in date order in the tuberculosis ward, and maintained by the health educators. Clinical notes of out-patients and in-patients were kept in patients' files, with summaries on small patient-retained cards which had been specially designed at Tintswalo. Books for recording expected and actual patient attendances, laboratory specimens and results, and HIV results were kept in the TB ward. They were not always complete, and not easy to use to identify non-attending patients and laboratory results. Treatment outcomes were not documented in any form.

12.2.6 Staff and other resources:

The staff responsible for tuberculosis management included the medical officer, who had other responsibilities, and was only available for two ward rounds per week and one outpatient clinic session in the tuberculosis ward. The weekly outpatient clinic lasted between 4 and 6 hours during which between 10 and 25 patients were seen. The ward was managed by a senior professional nurse and during 1993 was staffed by one other registered nurse, one enrolled nurse, one nursing assistant, and two nursing students. Nurses were rotated frequently, usually every 3 months. A senior professional nurse was responsible for community management of TB patients. In 1993 she also had responsibility for the ward while there was no ward sister appointed. The community aspect involved the follow-up of patients who did not keep their appointments, and the tracing of all contacts of all patients. Two male health educators each of whom had completed a 3 month course in TB, worked with this nurse. The tuberculosis ward and community service were accountable on the nursing side to the hospital nursing managers, and on the medical side to both the senior hospital superintendent and the community health specialist. There was no coordination of the community service.

Clinics had no role in tuberculosis management. Patients suspected of having the disease were told to attend the hospital for investigation. No tuberculosis treatment was given at clinics.

A hospital vehicle was usually available to the community team. During 1993, only one health educator was licensed to drive, so the two travelled together. The vehicle was often diverted for use in other services by the hospital nursing managers.

A formal study of drug supplies was not done, but during the study there were periods when drugs were not available in the hospital pharmacy. Patients then received courses of incomplete, separate drugs.

A system of applying for compensation for pneumoconioses in patients with and without

tuberculosis had been established. One of the educators was responsible for history taking, and for completing some of the documentation for these patients.

12.3 Conclusions

There were many aspects of the management of tuberculosis that were problematic.

* The information and recording system did not allow any description of patient profiles, the source of patients, bacteriological coverage, nor treatment outcomes
* There were no clear policies on diagnosis, with probable over-treatment of patients without tuberculosis based on radiological evidence
* There was no emphasis on smear positive cases of TB
* There was no system for tracing non-attenders
* Drug treatment usually used recommended drugs, but as separate drugs, self-administered with no DOTS, supplied for many months at a time
* A community tuberculosis team existed, but operated without clear direction, without a dedicated vehicle for visits
* There was no integration of the tuberculosis service at clinic level

However, there were many staff members available, and potentially many professional nurses at clinics, who could provide a better quality, more accessible service to patients.

The next stage of the study:

A detailed record review of patients admitted to the tuberculosis unit of Tintswalo hospital since the 1st of January 1992 started in mid-1993. This was with the permission of the Gazankulu Director-General of Health, Dr Paul Robert, the consent and cooperation of the Tintswalo hospital management and tuberculosis ward staff, and after clearance from the University of the Witwatersrand Committee for Research on Human Subjects. (Appendix B1) This review continued over the next 18 months until all patients in the two and a half year period until the 30th June 1994 had been studied. The methods and results of that review are the subject of chapter 13.

CHAPTER 13

A RECORD REVIEW OF PATIENTS WITH TUBERCULOSIS ADMITTED TO TINTSWALO HOSPITAL IN THE PERIOD JANUARY 1992 TO JUNE 1994

This chapter includes:

Objectives

Methods

Results

Discussion

Conclusions

Recommendations

13.1 Objectives

To describe patients admitted to the tuberculosis unit at Tintswalo hospital during 1992, 1993 and the first half of 1994 in terms of:

* Admission numbers, types and duration of hospital stay: Number per month and year, new or recurrent admissions, length of stay in hospital.
* Patient characteristics: Age, gender, and distance from village of residence to hospital
* Clinical features and diagnostic criteria used: Type of disease, HIV status, number with pulmonary disease who were smear positive, culture positive, or not bacteriologically proven
* Patient management: treatment outcomes, patient attendances
* Relationships between treatment outcomes and the following variables: patients' ages and genders, first or repeat admission, duration of admission, distance between hospital and patients' homes

13.2 Methods

The study was a cross-sectional record review.

Study Population:

All patients admitted to the tuberculosis unit between the 1st of January 1992 and the 30th of June 1994 were included. Admission to the unit did not necessarily mean admission to the ward, as some patients were managed as out-patients for the entire duration of their treatment.

Exclusions:

The records excluded from those studied were firstly those of **child contacts** who were on chemoprophylactic treatment. Their removal confined the study population to patients with diagnosed tuberculosis. The process of exclusion involved a scrutiny of files of all patients under the age of 16 years to examine the clinical findings, results of skin, bacteriological and radiological tests. Where a child was stated to be a contact of a TB case, and where the recorded clinical, bacteriological, X-ray and skin tests in combination did not point to a diagnosis of active TB disease, or where the notes specifically indicated that the child was on prophylactic treatment, the record of that child was omitted from the data set. There were 93 such child contacts whose exclusion left a study population of 514 individuals.

The second category of records excluded were those of patients who started treatment, but were subsequently discharged by the ward doctor as "not TB".

Sample

No sample was taken. Every patient fitting the population criterion was included.

Measurements:

As the national tuberculosis register was not introduced to this district until July 1994, all

information had to be collected from patients' files. A questionnaire was designed on the public domain software package Epi Info version 6 (CDC Atlanta, Georgia). Information on each patient was entered into this programme from the patient's file kept in the tuberculosis ward. Considerable effort went into identifying all the patient files.

Numbers of patients admitted to Mapulaneng and Matikwane hospitals were collected by counting those noted in ward admission books at each of those hospitals.

The distance from each patient's village to Tintswalo hospital was measured from a large scale map (1:50 000). Distance categories were defined as "close" to the hospital (up to 9 kilometres), "intermediate" (10 to 25 kms), "far" (26 to 49 kms, and "very far" (50 kms or more). This last category included places that were outside the boundaries of the Tintswalo health ward (as it was then called).

During 1992 and 1993, most patients were routinely tested for HIV (after their informed consent). During 1994 patients were tested on clinical suspicion only. Results were not available in all files. Every attempt was made to determine the result for every patient by searching through ward files, laboratory records and by consulting the community health doctor to whom results were sent first. Absent results could have meant that those patients had not been tested, or perhaps that the result was negative and, being less important, was not entered in the patient file.

New patients were defined as those who had not had a previous course of treatment.

At the time of this study, South Africa was not using the internationally accepted treatment outcomes formulated by the WHO. Those used in this study were specifically formulated, and were the same as WHO recommended outcomes, excluding "cured" outcomes, which required proof of sputum bacteriological conversion. Every hospital attendance of each patient was documented, and the treatment outcome coded for each according to the

following criteria:

Completed treatment - patients returned on the date or within two weeks of the date of each appointed follow-up visit to the hospital, and were pronounced cured by the medical officer of the ward. Cure was on clinical and radiological criteria. No final sputum bacteriology was done on pulmonary cases.

Treatment not completed (interruptors) - patients who failed to return within two weeks of their scheduled appointments. A subgroup of this category were those who never returned after discharge from hospital.

Died - patients who died during the course of treatment. This outcome was dependent on the notes in patients' files. The exact cause of death was not determined.

Transferred - patients formally transferred to another treatment place outside the district.

Study Limitations:

* Data relied on patient records some of which were incomplete.
* There was no measure of patient adherence other than their attendance on appointed dates. The "completed" treatment category was a best estimate, since drugs for a two or three month period were taken home without monitoring of any kind. There may well have been many more interruptors than this assessment was able to measure.
* Two weeks of missed treatment for interrupters was an over-generous period, which probably resulted in an overestimation of the completed treatment category, and an underestimate of interruption.
* Since no bacteriology was done at the end of treatment, neither cure (conversion from positive to negative smear) nor failed treatment (smear positive at the end)

could be documented.

* The distance from patients' villages to Tintswalo hospital was an estimate of the exact distance from their homes, but judged to be a fair estimate.

Ethical issues:

The study received clearance from the Committee for Research on Human Subjects of the University of the Witwatersrand (clearance certificate - appendix B1). Complete confidentiality of patient records was maintained.

13.3 Results

Summary:

* *There were 514 patients admitted during this period, mainly adult males. Almost one quarter (23%) lived more than 25 kilometres from the hospital.*
* *Sixteen percent were recorded as having had treatment for tuberculosis at some time in the past.*
* *Over 90% had pulmonary tuberculosis, only half of these were known smear positive. There was a significantly higher proportion of patients smear positive in the last 6 months of the period (67%) compared with the first two years (50%).*
* *Fifteen percent of all patients were not admitted, half of these were children. Sixty five percent of those who were admitted spent up to 4 weeks in hospital.*
* *Sixty percent of all patients completed their treatment. For new smear positive patients the rate was 67%, if the small number of patients transferred elsewhere was excluded. This estimate of "completed" treatment was a best estimate only, as patients were given several months' drug supplies to take at home, unmonitored and unsupported. It is possible that completed outcomes were as low as 44%.*
* *Forty four patients died of TB, giving a case fatality rate of 9%.*
* *One quarter of all smear positive patients interrupted their treatment. This figure may in fact have been almost half of all patients.*

* *A significantly lower completion rate was associated with a greater distance from the treatment point; only half the smear positive patients who lived more than 50 kilometres from the hospital completed the full course of treatment.*

13.3.1 Response rate:

Results were available for 513 of the 514 patients, except for a few variables as will be indicated. The file of one patient was missing; only that patient's treatment outcome was known. Missing information for some variables represented a small proportion of the total, and there was no reason to believe that bias was introduced in any way.

13.3.2 Patient numbers:

Five hundred and fourteen patients were diagnosed as tuberculosis in the period, giving a mean annual admission rate to the unit of 206 patients.

Admissions per month:

In 1992 there were 248 cases admitted, in 1993, 186 and in six months of 1994, 78 (if the 1994 figure for 6 months was extrapolated for the year, 156 admissions could have been expected). Higher numbers were admitted in spring months, with a mean over the whole period of 17 cases per month.

Estimates of admission rates in Mhala and Bushbuckridge:

Population estimates for 1993 for the Mhala health ward and for Bushbuckridge respectively were 230 000 and 500 000 (background chapter 11). Tuberculosis admissions to Tintswalo hospital were 186 in 1993. For Mapulaneng and Matikwane hospitals, figures were 539 and 92 respectively. Measured admission rates in 1993 for the Tintswalo ward and for the whole were thus 81 per 100 000 for Mhala, and 176 per 100 000 for Bushbuckridge.

13.3.3 Patient characteristics:

Two thirds of the patients, 344, were males and one third, 170 females.

The age distribution is presented in table 5. Categories were defined to describe the proportions of young children (the under-6 years of age category is used in the South African tuberculosis control programme guidelines for childhood disease), older children (6-14 years), young adults (15-29 years), older adults (30-59 years) and the elderly (60 years or more). Patients admitted with tuberculosis in this district were mainly adults, with 84% (404 patients) over the age of 15 years. Nineteen percent were over 60 years.

TABLE 5: AGE DISTRIBUTION OF PATIENTS (1992-1994)

Age group in years	n	%
0-5	44	9
6-14	35	7
15-29	103	20
30-59	233	45
60+	98	19
Total	513	100

This age distribution was compared with that of the general population, for which a study of 97 households (650 people) in the district in 1993, revealed 34% under 15 years of age, 38% 15 to 29 years, 21% 30 to 59 years and 7% 60 years and over.[387]

13.3.4 Distance from Tintswalo hospital:

Table 6 shows the frequency distribution of distance from patients' homes (their villages) and the hospital. For 23% the hospital was more than 25 kilometres distant.

TABLE 6: DISTANCE FROM TINTSWALO HOSPITAL FOR 1992-1994 PATIENTS

Distance from Tintswalo hospital (Kilometres)	n	%
Up to 9	182	36
10-25	213	42
26-49	77	15
50+	39	8
Total	511*	101

* no addresses for 3 of the 514 patients

13.3.5 Previous admissions:

According to the records, 82 (16%) of the 512 patients with any information in their files had been on treatment for TB at some time in the past.

Twelve patients had documented readmissions within the two and a half year study period.

13.3.6 Length of stay in hospital:

Dates of admission and discharge were not available for 36 patients (7% of 514). Exact dates of admission and discharge were not always accurately documented in patients' files. There was often a discrepancy between the dates in files and in the ward admission book. Results are therefore subject to error, but give an indication of the duration of hospital admissions. The

range of admission period for those who were admitted was 1 day to 217 days, with a median of 15 days, a mean of 22 days and a mode of 0 days - most patients (72) were not admitted. The duration of hospital stay for 478 patients is given in table 7.

TABLE 7: DURATION OF HOSPITAL STAY, 1992-94 STUDY

Period in hospital (days)	n	%
Nil	72	15
1-7	60	12.5
8-14	98	20.5
15-21	67	14
22-28	56	12
More than 28	125	26
Total	478 *	100

* excluding 36 for whom dates were missing

Fifteen percent of patients were not admitted. Over half of those (38 or 53%) were under 15 years of age, and 37% under 5 years of age. Only 7% of patients over 60 were not admitted. None of the patients who were not admitted were HIV-infected.

Of the 406 who were admitted, 158 (39%) spent up to two weeks in the ward, 123 (30%) up to 4 weeks, and the remainder, 125 (31%), had a period of admission exceeding 1 month.

Those patients who spent less than 29 days in hospital were compared with those who stayed 29 days or more for age and distance from hospital.

In table 8 age and duration of hospitalisation is shown.

TABLE 8 : DURATION OF HOSPITAL ADMISSION AND AGE OF PATIENTS (1992-1994)

Duration (days)	Age in years					Total
	0-5	6-14	15-29	30-59	60+	
0-28	36(10%)	29 (8%)	79 (22%)	149(42%)	60(17%)	353
29+	8 (6%)	6 (5%)	19 (15%)	67(54%)	25(20%)	125
Total	44 (9%)	35 (7%)	98 (21%)	216(45%)	85(18%)	478

Patients 30 years of age and more were more likely to spend more than 4 weeks in hospital (X^2= 8.18; df1; p=0.004). However the majority of those over 30 spect less than 28 days in hospital.

Males were not more likely to be admitted for more than 4 weeks (X^2=0.63; df1; p=0.43)

Those who spent more than 28 days in hospital were more likely to **live further away** from the hospital (X^2 for linear trend=6.8; p=0.009), as shown in table 9.

TABLE 9: DURATION OF HOSPITAL ADMISSION AND DISTANCE FROM HOSPITAL (1992-1994)

Duration	Close 0-9 kms	Intermed. 10-25 kms	Far 26-49 kms	Distance 50+ kms	Total
0-28 days	130 (37%)	150 (43%)	50 (14%)	21 (6%)	351
29+ days	36 (29%)	50 (40%)	23 (19%)	15 (12%)	124
Total	166 (35%)	200 (42%)	73 (15%)	36 (8%)	475 *

* information on duration and distance was not available for 39 patients

13.3.7 Clinical features and diagnosis:

Ninety three percent (476) of the 513 cases were diagnosed with pulmonary disease, 5% (23 cases) had pleural effusions, 1% (6 cases) bone and joint TB, there were 3 cases each of cervical adenitis and abdominal TB, and 1 case each of TB meningitis and TB pericarditis. The diagnosis of primary disease was not made.

TB microscopy and culture tests and results:

TB smear testing was done at the local hospital laboratory and in addition at the regional (Pietersburg) or central (Johannesburg) laboratory of the South African Institute for Medical Research (SAIMR). Cultures for TB were sent to Pietersburg or to Johannesburg. Faxed results from these centres were often sent via a third laboratory at Phalaborwa, a Northern province town 120 kilometres north of Tintswalo hospital.

Microscopy:

Of the 476 cases of pulmonary disease, 252 (53%) were smear positive, 134 (28%) smear negative and 90 (19%) had no documented results in the files, meaning they had not been tested, or that results were lost. Thus bacteriological coverage was 81%, and the smear positive rate 53%. Nearly half of the cases of pulmonary disease (47%) were registered with either negative or no results.

Cultures:

Thirty four percent of all cases had TB cultures performed in addition to microscopy tests. Table 10 analyses smear and culture results in more detail.

TABLE 10: SMEAR AND CULTURE RESULTS FOR PATIENTS WITH PULMONARY DISEASE, 1992-94 STUDY

Result	Culture Positive	Culture Negative	Culture Unknown	Total
Smear Positive	95 (38%)	22 (9%)	135 (53%)	252 (53%)
Smear Negative	2 (1%)	38 (28%)	94 (70%)	134 (28%)
Smear Unknown	0	2	88	90 (19%)
Total	97 (20%)	62 (13%)	317 (67%)	476 (100%)

Of the 252 smear positive cases, 117 (46%) had TB culture tests performed at the same time. Ninety five of the 117 (81%) were culture positive and 22 were culture negative. (possible reasons for this will be given in the discussion section of this chapter on page 141). Of the 134 smear negative patients, 40 (30%) had culture tests, of whom 2 (5%) were positive.

13.3.8 HIV status:

Those tested for HIV status were mainly adults; 97% were over the age of 14 years. Test results are presented in table 11.

TABLE 11: HIV RESULTS, 1992-94 STUDY

HIV result	No. of Patients	% of total	% of those tested
Positive	28	6	10
Negative	254	49	90
Unknown	232	45	
Total	514	100	

The HIV rate as a proportion of all tested was 10%. For patients admitted in the two year

period 1992 and 1993, this rate was 10%, for those admitted in the first 6 months of 1994 it was 9%. Twenty one patients (75%) were between 30 and 59 years of age, 5 between 15 and 29 years, and 1 in each of the under 6 year and over 60 year age groups.

HIV-positive patients were not more likely to spend more than one month in hospital. (X^2=1.4; df1; p=0.24).

13.3.9 Treatment Outcomes:

Treatment outcomes were assessed according to the criteria described in the methods on page 122. Outcomes for the 514 patients are given in table 12.

TABLE 12: TREATMENT OUTCOMES - all patients and smear positive cases (1992-1994)

Outcome	All patients n (%)	New smear positives n (%)
Completed	307 (60)	139 (67)
Interrupted	154 * (30)	52 (25)
Died	44 (9)	16 (8)
Transferred	9 (2)	2 (1)
Total	514 (101)**	209 (101)**

* 75 of the 154 interruptors (51%) had never returned after discharge from the hospital.
** percentages rounded

Patients transferred for treatment outside the district:

Nine patients were referred to another health service to complete their treatment. There were 3 females and 6 males, all over 15 years of age (all but 1 over 30 years). The places to which they moved and requested transfers were cities or towns in Gauteng (Johannesburg, Benoni, Westonaria) or Mpumalanga (Nelspruit, Hoedspruit), or to hospitals in districts of the

Northern Province (Mapulaneng and Maandagshoek). For one patient there was no information.

When transferred patients are removed from the table of outcomes of all patients, the completion rate becomes 61%.[307, 505]

New smear positive patients:

In line with the accepted method of evaluating a tuberculosis service, the treatment outcomes of 209 smear positive patients who started treatment for the first time (new cases) were measured. These results are included in table 12. Sixty seven percent of new smear positives completed treatment. Removing the two transferred out from the new smear positive cases leaves the completed rate unchanged.

The rate of interruption decreased during the two and a half year period, with 46 patients (26%) interrupting in the two year period 1992 and 1993, and 6 (18%) in the first 6 months of 1994.

There were 44 deaths recorded, 16 of these in smear positive patients.

Some assumptions have been made to adjust completed and interrupted rates to more realistic figures.

Completed treatment

estimated 60% of 307 documented		184
estimated 50% of 75 non-returners		37
estimated 40% of 9 transfers	3	
Total		**224 (44% of 514)**

Interrupted treatment

estimated 40% of 307	123	
estimated 50% of 75 non-returners		38
documented interrupters (154-75)		79
60% of 9 transfers		6
Total		**246 (48% of 514)**

Died (as documented) 44 (9% of 514)

13.3.10 Outcomes compared with a number of variables:

The results of comparing outcomes with a number of variables (sex, age, first or repeat admission, the duration of admission, and the distance between patients' homes and the hospital) will be described. Those patients transferred out will be excluded, so that the denominator will be 505 for the total number, and 207 for new smear positives.

Sex and outcome:

Treatment outcomes by sex are shown in table 13.

TABLE 13: TREATMENT OUTCOMES AND SEX - ALL CASES (1992-1994)

Sex	Completed	Interrupted	Died	Total
Female	102 (61%)	53 (32%)	11 (7%)	166 (33%)
Male	205 (60%)	101 (30%)	33 (10%)	339 (67%)
Total	307 (61%)	154 (30%)	44 (9%)	505 (100%

Females were not more likely to complete treatment (X^2=0.04; df1; p=0.83), nor to die (X^2=1.35; df1; p=0.25). When deaths were excluded, there was still no difference (X^2=0.07; df1; p=0.79).

Results for new smear positive patients are shown in appendix A1. There were no differences in treatment outcomes between sexes.

Age and outcome:

Table 14 shows treatment outcomes for different age categories for all patients.

There were significantly more deaths in those over 15 years (X^2=6.3; df1; p=0.011), but no more likelihood of patients under 15 years completing treatment (X^2=0.05; df1; p=0.82), nor under 30 years (X^2=0.27; df1; p=0.6), nor under 60 years (X^2=1.08; df1; p=0.29). When deaths were excluded, there remained no association between age groups and outcome. The results for new smear positive patients show no significant differences in deaths in different age groups, nor in completed rates. The numbers per group were small. This table of results is to be found in appendix A2.

TABLE 14: TREATMENT OUTCOMES AND AGE - ALL CASES (1992-1994)

Age group (years)	Completed	interrupted	Died	Total
0-14	49 (62%)	29 (37%)	1 (1%)	79 (16%)
15-29	64 (63%)	31 (30%)	7 (7%)	102 (20%)
30-59	140 (62%)	66 (29%)	21 (9%)	227 (45%)
60 +	54 (56%)	28 (29%)	14 (15%)	96 (19%)
Total	307 (61%)	154 (31%)	43 (9%)	504* (100%)

* excludes 9 transferred cases and 1 of unknown age

New (first) and readmissions and outcome:

Table 15 shows the results of treatment outcomes for new patients and readmissions.

TABLE 15: TREATMENT OUTCOMES AND FIRST/ REPEAT ADMISSIONS, ALL CASES (1992-1994)

	Completed	Interrupted	Died	Total
Readmission	47 (59%)	26 (33%)	7 (9%)	80 (16%)
First Admission	259 (61%)	128 (30%)	36 (9%)	423 (84%)
Total	306 (61%)	154 (31%)	43 (9%)	503* (100%)

* excludes 9 transferred cases and 2 for whom admission details were missing

Readmitted cases were not less likely to complete their treatment ($X^2=0.17$; df1; $p=0.67$). Results were unchanged if deaths were excluded. Of the 12 patients who were readmitted within the period of this study, 8 had interrupted their treatment in the first admission, and 4 had completed.

Hospital admissions and outcome:

Outcomes for patients and whether they were admitted to hospital or not are shown in table 16.

TABLE 16: TREATMENT OUTCOMES AND HOSPITAL ADMISSION (1992-1994)

Admission to hospital	Completed	Interrupted	Died	Total
No	44 (62%)	27 (38%)	0	71 (16%)
Yes	262 (68%)	124 (32%)	12 (3%)	386 (84%)
Total	306 (65%)	151 (32%)	12 (3%)	469 (100%)

Treatment was not more likely to be completed in those who were admitted (X^2=0.39; df1;p=0.53). The lack of difference remained even when patients who died were excluded. (X^2=0.94;df1;p=0.33)

Outcomes for different periods of admission for all 469 patients with known admission dates appear in table 17. The effect of different periods in hospital was measured by studying the outcomes for the 398 patients admitted for different periods (excluding 71 not admitted). Completed treatment was more likely (just not statistically significant) for those who spent more than one week in hospital cpmpared with all otehr periods (X^2=3.68; df1; p=0.05), but not for any period more than 14 days (X^2=0.13; df1; p=0.72).

TABLE 17: TREATMENT OUTCOMES AND PERIODS OF ADMISSION (1992-1994)

Duration of admission (days)	Completed	Interrupted	Died	Total
0	44 (62%)	27 (39%)	0	71 (15%)
1-7	46 (77%)	14 (23%)	0	60 (13%)
8-14	59 (61%)	36 (37%)	2 (2%)	97 (21%)
15-21	44 (68%)	18 (28%)	3 (5%)	65 (14%)
22-28	35 (64%)	19 (35%)	1 (2%)	55 (12%)
More than 28	78 (64%)	37 (31%)	6 (5%)	121 (26%)
Total	306 (65%)	151 (32%)	12 (3%)	469* (101%)

* excludes 8 patients transferred elsewhere

Distance from hospital and outcome:

Treatment outcomes according to distance categories from patients' homes to Tintswalo hospital (based on the approximation of village to hospital) are shown in table 18.

TABLE 18: TREATMENT OUTCOMES AND DISTANCE FROM HOSPITAL (1992-1994)

Distance in kms	Completed	Interrupted	Died	Total
0-9	114 (63%)	50 (28%)	17 (9%)	181 (36%)
10-25	131 (62%)	62 (30%)	17 (8%)	210 (42%)
26-49	44 (59%)	24 (32%)	7 (9%)	75 (15%)
50 +	15 (41%)	18 (49%)	4 (11%)	37 (7%)
Total	304 (60%)	154 (31%)	45 (9%)	503* (100%)

* *excludes 8 transferred cases and 2 for whom address information was missing*

There was a significantly greater chance of not completing treatment in patients who lived more than 50 kilometres from the hospital (X^2=6.6; df1; p=0.01).

For **new smear positive patients,** results were similar, with a significantly greater proportion of patients not completing if they lived very far from the hospital. These results are shown in appendix A3. Patients living within 25 kilometres of the hospital were more likely to complete their treatment (X^2=4.09; df1; p=0.04). When deaths were excluded, 9 of the 17 patients living more than 50 kilometres distant (53%) interrupted.

13.4 Discussion

This subsection will review the numbers, sex and age distribution of admissions, the diagnostic criteria, the type of disease and HIV-infection, then management in terms of outcomes, and any variables associated with outcome. International and local South African experiences will be compared, as well as reasons cited for successes and problems.

Patient Admissions:

Numbers and rates: The number of admissions in 1992 was 248, similar to the recorded admission numbers for 1989, 1990 and 1991. There were fewer admissions to the tuberculosis unit in 1993 and 1994. Possible reasons were the influence of the research team who encouraged stricter diagnostic criteria with emphasis on bacteriological confirmation before starting treatment, and the exclusion of contacts on prophylaxis. However the declining admission rate to Tintswalo hospital is not easily explainable, especially in the face of the known rising prevalence of HIV-related disease, and the known breakdown of the services of the neighbouring district hospital, Mapulaneng.

Tuberculosis notifications for Gazankulu for 1992, numbered 598, and the population 1 million.[389] Even if the tuberculosis incidence rate had been half the national average for the black population (100 per 100 000), 1000 cases would have been expected for the homeland population of 1 million. Tintswalo, as one district of the whole province, contributed 252 cases, 42% of the Gazankulu total, which meant that either Tintswalo's data was not reaching the collation centre of the Department of Health, or that most other districts were not reporting cases, or both these possibilities.

For developing countries, for every 1% annual risk of infection, an average of 50 cases

of smear positive disease per 100 000 population will occur.[59] In Sub-Saharan Africa the annual risk of infection is 1.5-2.5%.[39] If the risk in the Mhala area were estimated at 1%, and the population 230 000, there would be an estimated 115 cases of smear positive disease per year. Based on the formula 1.22 cases of smear negative and extrapulmonary disease for every smear positive,[28] there would be a further 140 cases per year, bringing the annual incidence in this area to 255, close to the actual 1992 admission figure, but more than the 186 and 156 for 1993 and 1994 figures , the latter extrapolated for the whole year. Admissions figures include previously treated cases and do not reflect true incidence of disease in the community. Some cases probably present at other health or traditional services, some may not present at all.

If estimates for the population of 500 000 in Bushbuckridge are used, the annual number of smear positive cases calculated from the 50 smear positives per 100 000 population for a 1% annual risk of infection is 250. The total number of tuberculosis cases based on the ratio of 1.22 : 1 smear negative and extrapulmonary to smear positives would be 555. In 1992, 879 cases of tuberculosis were admitted to the 3 hospitals of the sub-region. Figures for Mapulaneng and Matikwane were obtained from ward registers of those hospitals. They would include readmissions, and probably include patients on chemoprophylactic treatment (contacts).

It is not possible to draw any conclusions about the incidence, nor prevalence of tuberculosis in the general population from these hospital admission figures.

Sex: The preponderance of males with tuberculosis has been reported nationally,[390] in specific areas of South Africa,[343, 344, 347, 352] and in other countries.[78, 391] The reason for the difference is unclear, but may be related to gold mining activities of men (silicosis being a known risk factor for tuberculosis), to predominantly male habits (in rural areas) of alcohol abuse and

cigarette smoking, and also to the increased risk of spread of the disease in overcrowded urban environments, to which rural men, more than women, migrate in search of work, returning home when sick. To what extent women with disease may not have presented to health services, for cultural or family or other reasons, is unknown. A recent review of world literature on the subject has highlighted the fact that men's disease rates are higher than women's after the age of 15 years, and questions whether this is due to under-reporting in developing countries.[392] In this study, sex was not related to treatment outcome.

Age: Tuberculosis has been shown in many studies to be a disease of adults. In this study 65% of patients were in the economically active group (15-59 years of age). Only 16% of all patients in this period were under the age of 15 years, in contrast to 34% of the population in this age category. There were concerns that there may have been an under-diagnosis in children, in whom diagnosis can be difficult even in specialist hands. Less experienced and very busy clinicians at this hospital may have missed cases. Age was unrelated to outcome, except that older patients were more likely to die.

Bacteriological testing: In a tuberculosis control programme, smear tests are the essential investigation, culture testing for confirmation is unnecessary and wasteful of resources. In these results almost half of all smear positive cases had culture test results documented. More were done according to staff, who admitted that culture results were frequently not available, nor correctly documented. Doctors were said to suspect the results of the local hospital laboratory, although no action was taken to investigate or correct problems by organising quality control and retraining of the staff. The problem appeared to reside in the fact that this was an old "Gazankulu" laboratory without links to the SAIMR, with no quality control and

no support or continuing education for the laboratory staff.

The proportion of smear positive pulmonary disease was 50% in the first two years of this study, and 67% in the last 6 months. The change represents a change in practice with more emphasis on smear results.

Overall bacteriological confirmation was achieved in only 53% of pulmonary disease cases, far below the accepted programme standard of over 70%.[69] Ten percent of patients with bacteriological results were smear negative and culture negative. Almost 20% of all cases of pulmonary disease did not have any bacteriological tests. They represent an underutilization of smear testing, and probably over-treatment of non-diseased people. Every patient had at least one chest radiograph, many had large numbers during the course of treatment. This method was overused as a means of diagnosis. It would seem that a proportion of patients were not suffering from active tuberculosis.

There is an inconsistency in the fact that 22 smear positive patients had culture negative results. This may represent problems with microscopy techniques (false positives), delay in transportation of specimens sent elsewhere for culture resulting in non-viability (false negative culture) or perhaps mycobacteria other than tuberculosis (MOTTS) which were cultured, but recorded as negative results for *Mycobacterium tuberculosis.*

There was no evidence of any system or policy for diagnosis of tuberculosis from these results.

Disease type: Most of the tuberculosis disease was pulmonary. There was only one case in the study period of tuberculous meningitis. The internationally calculated ratio of 1 case of meningitis per 12 smear positive cases,[321] as well as that for South Africa of 1:120[322] did not fit this very low rate of tuberculous meningitis. Some of the less common clinical types of disease may have been missed by young, relatively inexperienced medical officers. The single case of tuberculous pericarditis was diagnosed by a visiting physician.

HIV-infection: This study could only measure the positive rate of those tested, and assumed that all results of those tested were filed. Most of the 1992-93 patients had HIV tests, but during 1994 patients were tested on clinical suspicion only. The overall rate is therefore not an accurate assessment of HIV status, although the 10% for 1992 and 1993 is probably a reasonable estimate. The HIV rate would be lower if unknown results were negative. Those testing positive were mainly in the sexually active age groups.

South African national antenatal sentinel-sites HIV-infection rates for 1992, 1993 and 1994 were 2.4, 4.2, 7.6 respectively.[393] The 1994 rate for the Northern Transvaal, (before the incorporation of the northern homelands to form the Northern Province) was 3.04, lower than the national mean. Higher rates are observed in patients with tuberculosis because of the opportunistic nature of this disease in HIV-infected persons. Hlabisa, a district hospital in KwaZulu Natal, measured a 10% HIV prevalence in tuberculosis patients for the period 1991-1993, and a neighbouring secondary hospital measured 14% in 1992.[394] Rietfontein hospital, a tertiary referral urban-based institution, reported a positive rate of over 30%. (personal communication, Directorate of HIV and Communicable diseases, Gauteng). Elsewhere in Africa reported HIV-infection in tuberculosis patients ranged from 30-66%.[43]

Treatment outcomes:

The absence of bacteriological testing at the end of patients' treatment meant that neither cure nor failure could be documented. This sub-section will discuss those patients who were transferred and who died, and will then address some of the issues around the completed and interrupted outcomes.

Transfers: There is some controversy about whether or not transfers out should be excluded from outcome analysis. WHO recommends that the district of origin should be in a position to determine outcomes. However it is widely felt in the South African context that assessment of such patients is not feasible. The transfer process must be formalised and personalised wherever possible, meaning that health professionals at the receiving end of patient referrals should be personally contacted with details about patients, and that patients should be urged to attend the referral services. Transferred patient numbers in this study are small (two percent of all outcomes), and the 9 patients have been excluded from analyses.

Deaths: Death rates of 9% of all cases (44 patients), and of 8% (16 patients) of smear positives are high compared with those reported from elsewhere in South Africa. There is known poor reporting and recording of deaths throughout South Africa.[316] It may be that the patients in this district had fewer, less accessible health services,and that they died of their disease. Severely ill patients may have presented to health services more readily. Another possibility is that this research process took care to determine whether or not patients had died. In fact a proportion, not quantified but large, of supposedly "lost" patient files when searched for and found, were of patients who had died. These deaths would not have been documented had the researchers not looked carefully. National surveillance data on case fatality rates for 1991 gave a figure of 4%,[313] while specific studies of the 1980s and early 1990s reported rates between 1% and 8%.(see table 3 on page 90) Higher rates of 7% for Hlabisa (354) and 8% for Kangwane[339] were reported from areas where death documentation may have been more accurate because it was more actively sought. Lower death rates for smear positive cases of 1% and 3% were found in 1996 in the Western Cape and Mpumalanga respectively.[312] International literature of the pre-HIV and AIDS era reports mortality rates between 1% and 8%, with the exception of rates in Bangladesh which reported 15%.[197]

It is difficult to measure deaths due to tuberculosis when this outcome category includes deaths from other causes. The new South African register for tuberculosis distinguishes between deaths due to tuberculosis and due to other causes.

The death rates recorded at Tintswalo hospital probably included some deaths from other causes. A study in Canada in the early 1980s reviewed 201 deaths among 1884 tuberculosis patients, including 48 diagnosed only after death and 153 who died while on treatment. Of the latter group, 56 had died of unrelated causes, in 67 tuberculosis was a contributing cause, and in only 30 was it the principal cause of death.[395]

Completed and interrupted outcomes: The measure of completed treatment was only a best estimate of that outcome, since the hospital policy was to prescribe drug supplies for two or three months at a time, with no system of monitoring adherence. Even if patients kept their appointments, there was no way of determining whether or not they had taken their treatment. A completed rate of 60%, and the smear positive rate of 67% were unacceptably low, and below the WHO target of 85% cure required to halt the progress of the epidemic. Rouillon has said that " the normal patient is one who defaults".[246] Thirty percent of patients failed to attend the hospital for further supplies of drugs. Half of those were never seen again. This high interrupter rate was serious risk for the development of drug resistance, especially those patients who continued to take some drugs sporadically. No treatment with high mortalities would have been preferable, in public health terms, to bad treatment which leads to chronic excretion of bacilli, often resistant to drugs.[56]

Treatment outcomes for this period could in fact have been substantially worse than originally measured assuming the estimated 44% completed rate.

Some international figures will be referred to in the ensuing discussion. These have already been presented in the chapter on Control Programmes, table 1, page 59.

Since the early 1980s, cure rates for smear positive cases for several country control programmes have been high. Examples are 92% in China,[223] 92% in Botswana,[229] 87% in Malawi,[226] and 82% in Tanzania.[221,222] Reasons given, as reviewed in section 1, chapter 7, page 62, were trained and supervised health staff, expert assistance including funding, political stability and good government policies related to health care, integration of tuberculosis services within other health services, and the vigorous implementation of Directly-Observed Treatment Short-Course (DOTS).

The deficiency of most of these factors in the South African, and specifically the Tintswalo situation, has been reflected in the tuberculosis problem in the country. There has been a lack of government commitment, and inadequate health service delivery for those at greatest risk of the disease. At Tintswalo there was no integration of the service within primary care clinics, and no DOTS. A university-health service project measured the pre-1980 completed rate at Tintswalo as 39%. After training and motivation of staff, information and education of patients, and attention to patients' needs such as reduction in waiting time at the hospital tuberculosis out-patient clinic, and after instituting DOTS,

the rate rose to 86% after 1983.[345] It is disturbing that Buch and his team managed high completion rates in the Tintswalo district eight years before this record review was done. It was clearly not a sustained achievement.

South African treatment outcomes from a number of studies, as well as those of the national surveillance data, have been reviewed in chapter 9, table 3, page 90. There were some good or fairly good completed rates from Emmaus district, where 92% of patients completed a

community-based DOTS programme in 1987-89,[352] from Mseleni, 85% completed rate in an intermittent treatment regimen without DOTS,[346] and a district of Ciskei, where 86% completion was achieved for decentralised clinic care including DOTS.[347] In the Hlabisa district, 74% of patients on a community-based DOTS intermittent regimen completed in 1991-1992, an improvement on the 18% before 1991.[354] Other reported results for rural areas are less good - 62% in the Charles Johnson hospital district,[342] 46% in Kangwane, previously a homeland, now part of Mpumalanga province,[339] and 28% in rural areas of the Estcourt district (348). Urban completed rates were generally worse, 22% from Kalafong,[334] 28% from Soweto,[343] 14% from DiepMeadow,[353] and 68% for a Western Cape suburb.[355]

A feature of these results is that most were the result of specific measurement, usually associated with interventions from interested individuals working in a district hospital. National figures differ from many of these figures, raising suspicion about accuracy of reported national rates. For 1991 this was reported to be 79% for all cases,[313] and for 1996 the new smear positive rate was 73%.[359]

Problems noted from a number of international and local studies (reviewed in detail in chapter 7) were staff shortages, poorly motivated and supervised staff, lack of transport for drug delivery and patient follow-up and poor health worker compliance with recommended treatment regimens.[194] War,[224] poor economic and political environments,[227,233,234] overcrowded urban conditions, as in Brazil,[227] and nomadic populations in Kenya[193] were further problems preventing completion of treatment courses. Individual patient factors quoted are homelessness, psychiatric illness, and drug addiction.[192]

South African studies have reported problems in the long distances between patients and

health services, health worker inadequacies, and lack of transport and systems of communication.[344, 345, 346, 348] Fragmented "homelands" are also a known constraint,[345] as is the high mobility of rural patients.[351] All these factors are well known in the Bushbuckridge subregion, and in most other rural areas of South Africa.

Risk factors for urban patients' interruption were being under 30 years of age in one Soweto study,[343] in another in the Western Cape, being under 5 years of age, as well as adolescence, being black, and being unemployed.[351] We found no association with age.

Nor was there any association between interruption and previous admission, although this has been demonstrated elsewhere.[286, 499] The previous admission rate of 16%, as stated by patients, may have been an underestimate for a number of reasons. The information was not always requested by nurses taking histories from patients, information may not have been recorded in the notes, patients may not have been aware of their diagnosis in past admissions, or may not have been willing to admit to previous admissions for fear of chastisement by hospital staff (whether unfounded or not). National surveillance readmission rates are between 8% and 15%,[395, 396] which may also be underestimates. South African research reports have described the proportion to be around 30%.[336, 396]

Outcomes were not influenced by admission to hospital. Those not admitted could have been a select group, less sick, or perceived to be more reliable, thus likely to adhere to treatment. They were mostly children, so that their treatment completion would have been determined by their mothers or minders. Nor were longer stays related to outcomes. One could have postulated that longer stays meant more exposure to information and education about the disease, and the need to complete a full course. This was not confirmed. Longer stays, on the basis of these results, should only be used for patients clinically unfit to be discharged.

One third of those admitted spent more than 4 weeks in hospital. The period under review in

this section of the study was before the use of the retreatment regimen which usually requires two months in hospital for daily parenteral streptomycin. Longer stay patients were older and lived further from the hospital. It was probable that their disease was more severe, and that they were less able to travel home or to manage independently. HIV-related disease was not found to be a factor in longer stays in this period. There are cost implications of providing long periods of secondary care as demonstrated by a study from a rural district hospital in KwaZulu Natal, where a short period in hospital (mean of 17 days), followed by community-based DOTS cost half that of two months initial hospitalisation.[198] The establishment of DOTS is critical, but for patients too ill to be discharged home, consideration should be given to the full utilization of health centres for a level of care between hospital and out-patient services. All hospitals should develop discharge criteria, and adhere to such policies.

Distance from hospital was shown by this study to be the only significant factor in determining treatment completion. There was a definite trend in less completion, with increasing distances from the hospital. Two thirds of all patients had to travel distances in excess of the original recommendation of King's "isocare lines" representing health services within 5 kms reach of community members.[397] The association with interrupted treatment is not surprising, as such travel is time-consuming, expensive and may be impossible if taxis or buses are not available. The association of distance and non-completion or non-adherence has been reported by others in other countries,[290, 292, 294] and in South Africa;[342, 344, 348] including Tintswalo in 1983.[345] Only one of the quoted studies measured distances. In Transkei in 1976, 48% of patients lived more than 10 kilometres from their treating hospital.[342]

13.5 Conclusions

This study of records of patients on treatment for tuberculosis at Tintswalo hospital during the period 1992 to mid-1994 revealed a number of problems.

- *Treatment outcomes were unsatisfactory, at best with 67% of new smear positive patients completing treatment, and probably far fewer. These rates are far below internationally accepted standards of cure of 85% of new smear positive patients. There was no measure of cure, since end of treatment bacteriology was not done. There was no DOTS, with the strong likelihood that drug resistance was developing in this district. The mortality rate was high, probably reflecting the serious nature of the problem.*
- *Disease diagnosis did not follow any criteria, and was dependent on a cumbersome system of sending specimens to different laboratories, some far distant, with unpredictability of results returning, and erratic filing of results in patients' records. Tuberculosis culture testing was done for new cases, causing unnecessary diversion of financial and other resources from other needs in the tuberculosis and other services at this hospital. The lack of policy and poor diagnostic system led to the probable over-treatment of individuals who did not have tuberculosis. The absence of focus on smear positive patients was of concern.*
- *The service for tuberculosis patients was centralised to the district hospital, and not integrated within the network of primary care clinics. Distance was shown to be a factor associated with poor completion rates, reflecting the inconvenience, and high cost for patients in money and time associated with travelling long distances for treatment.*

- *There was no registering and reporting system, with no means of monitoring or evaluating what was being achieved.*
- *Patient numbers and disease rate:*

  The number of patients, and calculated rate of tuberculosis did not appear to correlate with that expected from national figures, and especially from the level of poverty in the community.
- *Criteria for the duration of hospital admission should be drawn up, for the benefit of patients, and costs. Consideration should be given to using health centres for patients not necessarily needing hospital care, but not well enough for discharge.*

13.6 Recommendations

The study demonstrated the need for **establishing policies, diagnostic criteria and procedures, standardised treatment regimens, discharge criteria, treatment support in the community, and monitoring and evaluation** systems for tuberculosis services.

The implementation of these recommendations, and the measurement of their effect, formed the basis of the next phase of this research project. The intervention study that was set up will be described in section 3.

SECTION 3

THE INTERVENTION STUDY IN THE TINTSWALO DISTRICT

This section leads from the record review described in section 2, introduces the intervention study, and describes the methods used in the establishment of decentralised services for tuberculosis follow-up for patients living in villages served by sampled district clinics, and how processes and outcomes were measured. The rest of the section consists of results, discussion and conclusions. The chapters are:

14. Introduction, hypothesis, aim and objectives
15. Methods
16. Results
17. Discussion and Conclusions

CHAPTER 14

INTRODUCTION TO THE INTERVENTION STUDY OF 1994-96

This chapter includes:

Introduction

Study hypothesis

Aim

Objectives

14.1 Introduction

The record review described in chapter 13 took 3 months during 1993. The results were presented to hospital management and tuberculosis staff, and started a process of consultation and discussion with Tintswalo hospital management. Suggestions were that practices be changed to fall in line with guidelines of the WHO and the IUATLD, and that the hospital (district) policy be changed to decentralise tuberculosis follow-up treatment after discharge from the ward to district clinics. It would mean establishing diagnostic policies and procedures, standardised treatment regimens, the introduction of supported treatment (DOTS) in the community, referral of patients, on discharge from the hospital ward, to their nearest clinics for regular clinical assessment and for further supplies of drugs. Non-attenders should be followed up as far as possible by the clinic staff, but because of their lack of transport and their pre-occupation with treating other clinic patients, there should be a back-up follow-up system from the community tuberculosis team based at the hospital.

It was believed that diagnosis of tuberculosis at clinic level would be the next step in true

integration of tuberculosis case finding, as well as case holding, but that follow-up treatment was the first priority.

Initial reactions to the suggestions were mixed. Some doubted the capacity of the clinics to manage tuberculosis patients, and were unsure how it would work, others were confused about changing existing practices. Managers were not unsupportive, some were sceptical that decentralisation could work. Clinic nurses when consulted, expressed concerns about extra patient loads, but a ... that numbers of tuberculosis patients per clinic would be small.

Towards the end of 1993 it was agreed that a research project would be set up to implement the new decentralised system, and to measure the processes and the outcomes. There would be decentralised tuberculosis management at some district clinics, measurement of whether and how this could be achieved, as well as measurement of treatment outcomes. Comparisons would be made with those patients not receiving decentralised clinic treatment, but who continued to attend the hospital for follow-up.

If the system proved to be beneficial over a period of 2 years, hospital policy would implement decentralised tuberculosis treatment in all district clinics. If results showed that patient management at clinics was inferior to that at hospital, there would be evidence in favour of "selective" hospital-based tuberculosis management, at least until systems and quality of care at clinics could be improved.

Patients' attitudes towards, and opinions about the two systems would also be measured and taken into account.

National developments parallel to the research programme:

It is noteworthy that the study as described started at a time when there was no South

African tuberculosis programme receiving guidance and direction from international bodies. The "tuberculosis global emergency" had been announced in April 1993 and ideas were starting to filter through into South Africa.

In addition, the Tintswalo tuberculosis staff, together with the research team, agreed to assist the South African Medical Research Council Tuberculosis Research Programme to pilot a newly developed tuberculosis register, adapted for local use from the World Health Organisation's tuberculosis recording system.

This study was set up in the Tintswalo district to help establish internationally recommended procedures and practices for the diagnosis and treatment of tuberculosis, and to record the results. It further measured the processes and patient outcomes of decentralising tuberculosis services to some district clinics, and compared the outcomes with those of patients receiving hospital-based services. A system of tuberculosis treatment delivery was established in which **some district clinics (the treatment clinics)** would provide follow-up treatment for tuberculosis patients who lived in the area of those clinics. The post-hospital discharge management of patients living in the area of the **remaining clinics (control clinics)**, and for whom the **hospital was their closest health facility** would remain the responsibility of the district hospital, Tintswalo.

14.2 Study hypotheses

* Tuberculosis services can be successfully decentralised to district clinics
* Decentralisation of services will improve adherence to treatment and outcomes of TB patients
* Clinic staff will benefit in terms of satisfaction, credibility, community linkages and

professional knowledge from an extended role in management of tuberculosis, an important communicable disease with significant impact on the health of rural communities

* The process of decentralisation of tuberculosis services will focus attention on the organisation and delivery of district health services, and will ultimately contribute to information on district health systems development

The district health system was not being implemented in South Africa when the study started. District and provincial boundaries had not been finalised, so it was necessary for the researchers to define boundaries for the study area which would most probably coincide with the future decisions of district, local authority and provincial governments. Working as it did within the emerging district health system, the study was able to measure problems in implementation of district services in general, and in particular those for tuberculosis.

14.3 Study aim

The aim was to improve tuberculosis services in the Tintswalo district by standardising policies and procedures, and by improving service efficiency and accessibility to patients. Successful completion rates, namely cure (mainly) and treatment completion by 85% of smear positive cases, or at least approaching that target, as recommended by the WHO, was the ultimate goal.

14.4 Objectives

The specific objectives of this study were :

1. To measure characteristics of patients and their tuberculosis disease, over a two

and a half year period, 1st July 1994 to 31st January 1996, and to combine data from the earlier study (1992-1994) to provide a 4 year profile of patients.

2 To **monitor and document the diagnostic and treatment practices** for all tuberculosis patients admitted during the period 1st July 1994 and 31st January 1996, including:

diagnostic practices, duration of hospital stay, treatment support (DOTS), bacteriological monitoring of treatment, patterns of clinic and hospital attendance, treatment adherence as measured by patient card records, and by objective tests on a sample of patients

3. To measure and compare the **outcomes of treatment** for patients attending clinics and hospital:

   i) those receiving follow-up treatment at "treatment clinics" as defined

   ii) those living nearest to "control clinics" as defined, and receiving treatment at Tintswalo hospital

   iii) those for whom the hospital was the closest facility and who would attend there

   iv) those who were resident outside the study district boundaries, but chose to receive their treatment at Tintswalo.

4. To measure the knowledge, beliefs, attitudes and problems of each patient at various defined stages of their treatment

5. To **analyse treatment outcome** results for possible associations between patient and health service variables, in order to identify patient needs and problems, and any risks for non-completion of treatment.

6. To observe and document strengths and weaknesses in the process of **decentralisation** of tuberculosis services to district clinics, and to develop recommendations for the implementation of integrated tuberculosis services for this and other districts in South Africa.

CHAPTER 15

INTERVENTION STUDY METHODS

This chapter includes:

- *Study area*
- *Research staff*
- *Study Population*
- *Sample*
- *Measurements*
- *The Intervention Process*
- *Ethical issues*
- *Analysis*

15.1 The study area

The area defined for this study is illustrated in the map in figure 7 on page 159. It was the northern health district of the Bushbuckridge subregion of what was to become the Northern Province, according to the Constitution Act of 1996 of South Africa. The district hospital, Tintswalo, was responsible for 12 district clinics. The central and southern districts were to be served by Mapulaneng and Matikwane hospitals respectively. The northern boundary was the Orpen road from the Drakensberg mountains in the West to the Kruger Park in the East, the Western boundary was the Northern part of the (Transvaal) Drakensberg mountain range, and that on the East was the Manyeleti and Kruger National Game Reserves. The area covered 180 square kilometres. At the time the work started, the Southern boundary of the Tintswalo district had not been demarcated, so this boundary was defined for study purposes by a line drawn on a map in more or less the expected position of the boundary line. [It may happen that when a final decision is made on the Southern boundary line, that there is a difference

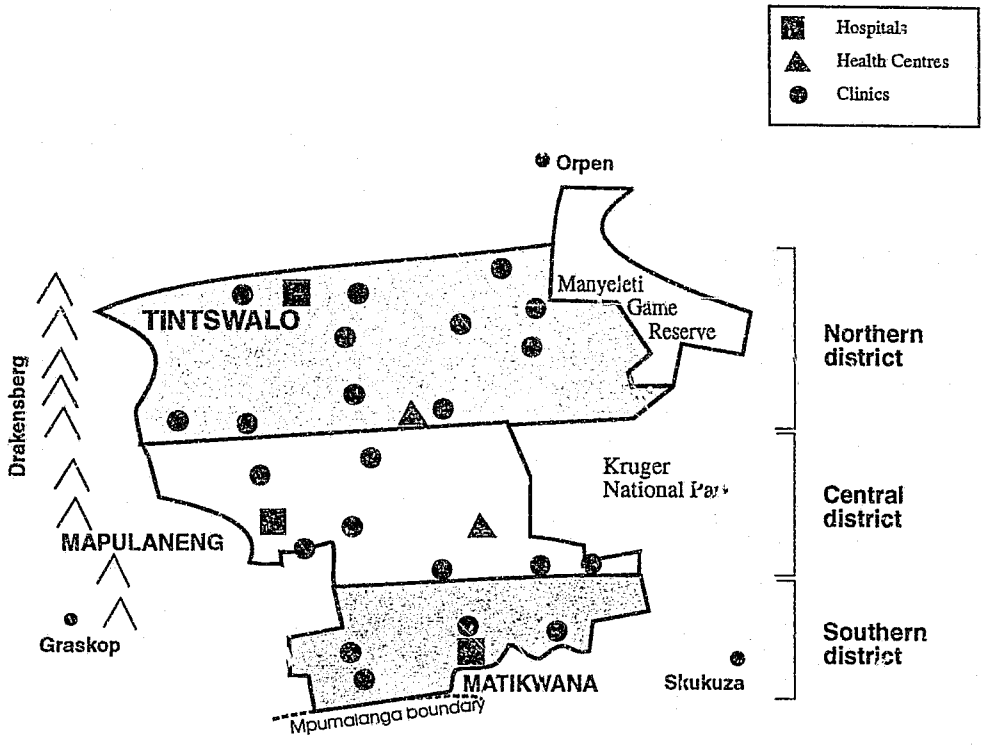


Figure 7: Bushbuckridge subregion showing new district demarcations

between that and the line drawn for this study. It is believed that there would be no change to the principles learned from the study.] The area served by Tintswalo hospital until 1995/96, when the health district began to be functional, was larger than the district described above, as it included the old Mhala district of Gazankulu, as well as areas which would become incorporated into the Mapulaneng district. Patients living outside the Tintswalo district were designated the "outside district" population for this study.

15.2 Staff of the research project

The research programme contributed to the knowledge and skills development in this rural area, by employing local individuals in the programme and providing training in **research methods** including data collection and analysis, individual and group interview techniques, **administrative methods** including the use of computers, office and general administrative procedures, and in **tuberculosis** awareness, knowledge and management using international and national guidelines. The team were mostly members of local communities in Bushbuckridge with good knowledge of the geography and the social environment of the area. The **research nurse** was seconded to the job for 2 years from Mapulaneng hospital, where she had gained experience in tuberculosis work. She had responsibility for the "intervention clinics", including the transfer of patients from hospital to clinics, organisation of drug supplies (taking packets to clinics), training staff in record keeping and in management of patients, facilitating the sputum monitoring system during treatment, and tracing non-attending patients. Collecting patient attendance data from treatment clinics was her special research task. She also participated in the group interviews.

Two interviewers, on contract research funded posts, conducted individual and group interviews, and performed urine tests to measure drug adherence. **A computer clerk**, recruited during the last year, had responsibility for collecting data on hospital patients, and for ensuring that all hospital and clinic patient data was computerised. A Wits University **community health registrar** on a 5-month rotation to the rural unit of the department of Community Health helped with clinic monitoring, and with nurse training. A British pre-medical **student** helped for six months with research vehicles, communication between the study area and Johannesburg, collection of laboratory reports, and the study of patient waiting times. The author was responsible for the planning and design of the study, negotiations with the health authorities, management of resources, staff training, monitoring, analysis and writing. She worked periodically in the tuberculosis ward as a clinician, and was the tuberculosis consultant for the hospital.

15.3 Study population

The study population was all patients diagnosed with tuberculosis and put on treatment at Tintswalo hospital during the study period. They lived within the Tintswalo district or outside those boundaries. Any patients transferred for follow-up treatment to Tintswalo from other hospitals were included.

15.4 Sampling

15.4.1 Determination of patient numbers:

Patients in the district were stratified into the three groups. The difference between the measured 60% completed treatment outcome from the 1992-1994 study, and the desired 85% after the intervention, was 25%. The sample in each category required to show that

25% difference was calculated to be 52 patients.(Epistat programme on EpiInfo 6.02, Centres for Disease Control and Prevention, USA and World Health Organisation 1994) The period of time required to collect data on 52 patients per group was estimated, using the admission figures from the previous study from 1992 to 1994 (as reported in chapter 13). The proportions of patients expected to live in each treatment group were calculated. Table 19 shows how this was done.

TABLE 19: CALCULATION OF SAMPLE OF PATIENTS IN DIFFERENT TREATMENT GROUPS

Study period	Treatment clinics	Control clinics	Hospital	Outside-district	Total patient numbers
1992-4 (30 mnth)	156 (31%)	123 (23%)	110 (22%)	122 (24%)	511 (100%)
Intervention (18 mnth)	93 (30%)	74 (24%)	66 (22%)	72 (24%)	305 (100%)

The 511 patients with known addresses, who had been admitted in the 30-month period of the earlier study were distributed according to treatment categories as shown.

It was calculated that during 18 months (60% of 30 months), 305 (60% of 511) patient admissions could be expected, assuming that the rate of admissions remained the same as for the earlier period. If the 305 patients were assumed to be distributed similarly geographically to the 511 of the earlier period, the numbers per treatment category would be 93, 74, 66, 72 patients for treatment clinics, control clinics, hospital and outside-district patients respectively. This meant that the required 52 per group would be achieved

within an 18 month period, even if the numbers were slightly less than in the earlier period.

The patients transferred from Mapulaneng and other hospitals were not included in these calculations as their numbers were expected to be small.

The data collection phase of the study started in July 1994, and continued until January 1996, for which month only those patients expected to complete treatment by the 31st July 1996 were included. A further month, August 1996, was spent tracing the last patients in order to complete the interviews for the study to be described in chapter 18.

15.4.2 Sampling of clinics:

There were 11 clinics and one health centre in the defined study area. The health centre was a larger facility in an urbanised area, and, although busier than most of the clinics, did not differ in function from them. The distribution of all registered tuberculosis patients for 1992 and 1993 was calculated. These numbers, together with the distance of each of the clinics and the health centre from Tintswalo hospital, were used to match pairs of clinics for expected numbers of patients and for distance. One of each pair became a treatment clinic, the other a control clinic. The process was one of random allocation, with stratification for numbers and for distance from hospital, six clinics, including the health centre, being selected as "treatment", where patients would receive treatment, and six as "control" clinics. Patients living in the area served by these clinics, would continue to attend Tintswalo hospital for treatment, as had been the policy for all patients until mid-1994.

Those patients for whom Tintswalo hospital was the closest health facility would receive their follow-up treatment at the hospital and be categorised as "hospital" patients.

The distribution and the names of clinics are illustrated in figure 8.

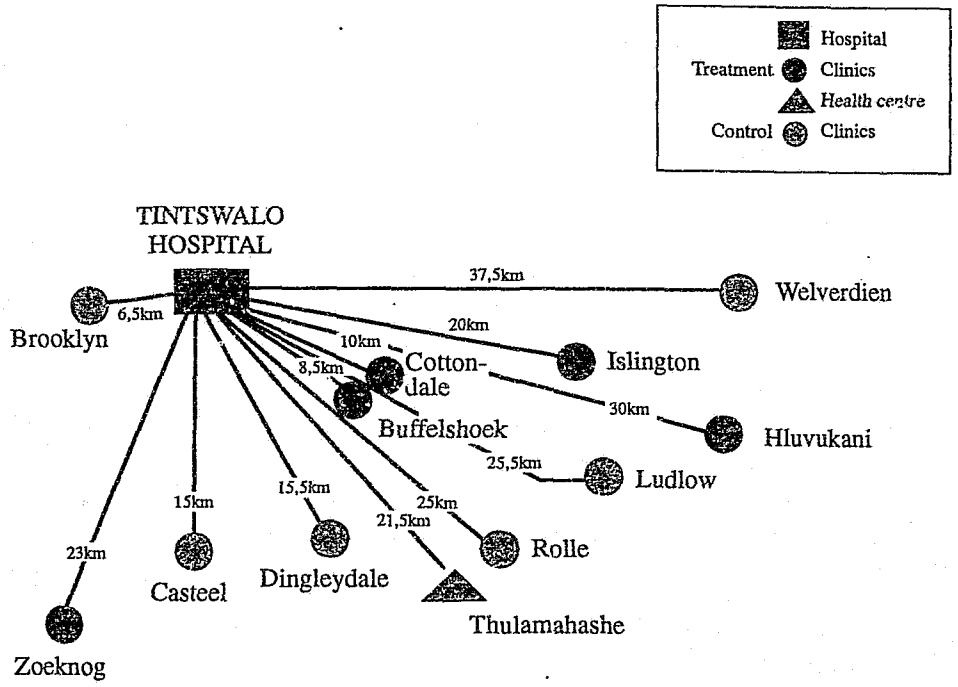


Figure 8: **Tintswalo district showing 11 clinics and one health centre, distance of each from Tintswalo Hospital and the allocation of clinics: treatment and control.**

Table 20 shows the figures on which the clinic randomisation process was based.

TABLE 20: SELECTION OF TREATMENT AND CONTROL CLINICS MATCHED FOR EXPECTED NUMBERS OF PATIENTS AND DISTANCE FROM TINTSWALO HOSPITAL

CONTROL CLINIC	Annual no. of cases expected *	Distance from Tintswalo hospital (kms)	MATCHED TREATMENT CLINIC	Annual no. of cases expected *	Distance from Tintsw. hospital (kms)
Brooklyn	13	6.5	Cottondale	12	10
Casteel	40	15	Buffelshoek	22	8.5
Dingleydale	8	15.5	Zoeknog	20	23
Ludlow	5	25.5	Thulamahashe	13	21.5
Rolle	26	25	Islington	11	20
Welverdien	12	37.5	Hluvukani	20	30
Total	104			98	

* based on earlier study figures

15.4.3 Treatment groups:

* **Intervention clinic patients** were defined as follows:

i) admitted to the tuberculosis unit of the hospital during the study period, 1st July 1994 to 31st January 1996, due for entry into the new tuberculosis register in that period

ii) patients for whom the "intervention" clinics were the nearest health facility, as determined by the research and hospital staff who knew the area well

* **Control clinic patients** were defined:

i) as i) above for intervention patients

ii) patients for whom the control clinics were the nearest facility as determined by the staff

* **Hospital patients**

  were those for whom the hospital was the closest health facility

* **Outside district patients**

  were resident outside the defined study area. They had chosen to attend Tintswalo hospital

Patients were not obliged to attend the treatment place allocated by the study methods. However, it would have been difficult for a patient not allocated to a treatment clinic to attend one, because referrals to clinics were carried out by direct transfer by the research nurse. She delivered each patient's course of drugs to the respective clinic, in a pack specifically labelled with that patient's name. If such a patient had requested to attend a clinic for treatment, arrangements would have been made to accommodate her or him.

Patients allocated for treatment at a clinic could have attended the hospital. This would have been noted.

15.4.4 Exclusions:

i) **Contacts on prophylactic treatment** who did not show evidence of tuberculous disease were excluded, even though they were sometimes registered in error. The number of child contacts under the age of 15 years removed from registered patient lists was 35. The record of each of those registered who were under the age of 15 was examined, together with the Xray to search for evidence of active disease.

ii) **Patients diagnosed "not tuberculosis".** There were 15 patients for whom the hospital medical officer made a decision that the diagnosis was not tuberculosis. They remained in the hospital TB register, but were not considered tuberculosis patients.

15.5 Measurements

All patients registered in the TB ward register were entered in a data set using a specifically designed questionnaire in the EpiInfo 6 programme of a personal computer. The questionnaire, included as Appendix C1, was an update on that used in the 1992-1994 study, and was similar to the tuberculosis register, which was not yet in use when this study started.

Entry of data onto the computer software was done by the research computer clerk who had some pre-existing computer skills, and who was given the specific training necessary within the project. The following variables were collected on each patient:

15.5.1 Basic demographic, address and clinical details:

The TB registration number, patient's name, age, sex, home address, source, category (whether new or retreatment patient), and international code of disease, as defined in the ICD-9, of every patient was obtained from the ward register.

The distances from patients' villages to Tintswalo hospital was measured on a 1 in 50 000 scale map. Although this was not an exact measure of the distances from patients' homes to the hospital, it was a close estimate thereof. The area was divided into geographic clusters which were arbitrarily defined, but with a basis in the ethnic distribution of people and in distance from Tintswalo hospital. These clusters can be seen in figure 12 in the results section on page 212, (since the figure includes patient numbers, it is presented in the results section). Areas 1 and 2 are closest to the hospital. Areas 4,6,7 and 9 were part of the previous Lebowa homeland and had a predominance of Sotho-speaking people. Area 3 was noted for its remoteness from the hospital and the Acornhoek village. Area 8, as part of the old Mhala health ward, was served by Tintswalo hospital. It is now part of the Mapulaneng district. Area

8, 9 and 10 (the latter including patients from places far North of the district) were outside the Tintswalo district.

Other information read from each patient's file was the date treatment started, date of discharge from hospital (from which the period in hospital was calculated), bacteriology results, the presence of multidrug resistance, and details of previous admissions.

Each patient's supporter was entered from information provided by either the research nurse (for intervention clinic patients) or the community team (for control clinic and hospital patients).

15.5.2 Clinic or hospital attendance:

Patients were due to attend either the hospital or their allocated clinic every month for assessment and to collect the next supply of drugs.

For hospital patients:

The research assistant stationed himself at the exit door of the ward every Tuesday when the tuberculosis clinic took place, and recorded the hospital attendance date of each patient attending that day. In addition the number of supporters' ticks on each patient card, representing patient days of treatment given under supervision, were counted and recorded. The data was then entered on the computer the same day.

For clinic patients:

The research nurse visited each of the six intervention clinics on a weekly basis to monitor the management of TB patients, to teach the staff about TB and the recording system, and to record dates of attendance of patients since the previous visit. She also documented the number of days that supporters had ticked on the patients' cards, as had

been copied by the clinic nurse onto the clinic-retained patient card. Data from the clinics was done on a form for each clinic designed for the purpose (appendix C2). The completed forms were given to the computer research assistant the day after each clinic visit for entry into the computerised records.

Validity checks:

Every entry was checked by the author for obvious errors, and a 10% sample of entries was checked every month using patients' hospital cards. On the author's 2-monthly visits to the six study clinics, a sample of clinic attendance dates were noted and checked against the entries in the computerised records. In addition obvious errors were identified on all entries, and checked.

Coding of attendance: The attendances at hospital or clinics of all patients were coded and entered by the author as follows:

For patients who completed treatment (or who were bacteriologically cured):

i) attendance monthly throughout the treatment period

ii) monthly attendance during the initial two months, thereafter only two or three monthly

iii) attendance two or three monthly throughout the period

For patients who interrupted treatment: (cumulative period of 2 months missed)

i) did not complete the first 2 months

ii) completed the first 2 months, missed a cumulative amount of 2 months thereafter

For patients who failed their course of treatment:

i) attendance monthly throughout

ii) attendance monthly for first 2 months, thereafter irregularly

iii) attendance irregular throughout treatment

15.5.3 Treatment adherence:

(i) Routine measure:

Adherence was "counted" from supporters' ticks for those patients who were supported. For those who were not, there was no way of measuring adherence except by asking the patient.

(ii) Urine testing

An objective method used on a sample of patients, was to test the urine of patients on treatment for INH metabolites. The test that was used used the principle that INH metabolites in the urine of a person taking the drug, either in combination or separately, are measurable by a colour reaction test. (Mycodyn Uritec, DynaGen, Inc, Cambridge MA, USA)

Pilot study: In order to test how long it would take for the test to become negative after a patient stopped taking the drug, a small pilot study was performed on ward patients. It was discovered that tuberculosis in-patients at Tintswalo had never been given drugs at the weekends (Saturdays and Sundays). This was not considered good treatment practice, but was utilised for the pilot study, and recommendations made to give daily treatment thereafter. There was a period of 60 hours from Friday morning when a dose of tuberculosis drugs was administered, until the next Monday morning, when the next dose was given.

Eight randomly selected adult patients, 4 female and 4 male, gave consent and submitted urine specimens over a weekend in August 1995. This pilot received clearance from the University of the Witwatersrand Committee for Research on Human Subjects. Appendix B2. All urine specimens from all 8 patients were tested every 4 hours by two of the

research team from the Friday morning before they received TB drugs, until they became negative, then again after receiving a dose on Monday morning until they became positive. Tests were done every 4 hours throughout each day; overnight specimens were refrigerated until tested early the next morning. Seven of the eight patients tested positive at the first testing, 24 hours after the last drug administration. One was negative because her specimen was water! The time from drug administration until a negative reading ranged from 28 to 44 hours, with a mean of 33.25 hours. All patients were again tested on the Monday morning from the time they received their TB drugs until the urine tested positive. This occurred 1 and 4 hours after the drug, with a mean of 2.7 hours.

Conclusions were that it took up to 44 hours after stopping the drug to become negative (mean 33 hours), and then up to 4 hours after starting treatment again to become positive (mean 2.7 hours). This indicated that a negative test under field conditions meant that the person has not had INH for between 1 and 2 days, and that the test would be useful to test patients' adherence to TB drugs.

Urine tests on a sample of the study population:

The sample of patients on treatment that was selected was those being interviewed after about 8 weeks of treatment. It was carried out during a five month period February to June 1996. Ninety five patients were sampled randomly, by placing pins in the weekly list of patients due for interviews that week. If the sampled patient was not available, the person next on the list was taken. Testing was either done at patients' homes or at the hospital when they attended the out-patient clinic. One of the interviewers was trained to do the tests. Patients' consent was obtained, and the test performed in front of them. Validity checks were done regularly by another member of the research team. Data was collected on a specially designed sheet, and included the name and TB number of the patient, the

date, time and test place, urine colour and test result. (Appendix C3) Every patient whose test was negative was retested within a few days, and the patient asked about adherence.

15.5.4 Treatment Outcomes:

The final treatment outcome at the end of treatment was coded by the author, according to the national register criteria:

Cured: *completed 6 months treatment for new patients or 8 months for retreatment patients, and has a negative sputum smear or culture at 2 months or at 5-6 months (new cases) or 7½-8 months (retreatment cases).*

Completed: *completed 6 months for new patients, or 8 months for retreatment*

Interrupted: *missed a cumulative period of 2 months treatment during the course*

Died: *died during the course, of whatever cause*

Failed: *remained smear positive at the end of the 6 or 8 months course*

Transferred: *patient transferred to another treatment point outside the area currently served by Tintswalo hospital*

Patient Interviews:

The methods and results of individual interviews conducted on each patient are described in chapter 18. Those of the group interviews form chapter 19.

15.5.5 Reasons for interruption:

Reasons for interruption were determined by the professional nurses responsible for each patient who interrupted. For intervention patients, it was the research nurse, for the remainder it was the community tuberculosis nurse.

A data sheet (appendix C4) was designed to document the results of visits to patients'

homes, and other attempts to trace them.

15.6 The Intervention process

The intervention was the establishment of the decentralised system of tuberculosis follow-up treatment at the six intervention clinics. This involved the following activities targeted at this treatment group:

* **Motivation and training of clinic staff to provide the knowledge and skills required.** Four formal training sessions was run for clinic staff, and every clinic visit of researchers was a training session.
* **Establishing a system when each patient was discharged from hospital.** This included a visit to the clinic for the patient to meet the clinic staff, be registered in clinic records, be given the next appointment date. The patient was then taken to the prearranged community supporter. Decisions about supporters were taken after asking patients who they would prefer, then visiting that individual to assess appropriatenes and willingness, before the patient was discharged from hospital. Exactly who supporters were, will be presented in the results.
* **Monitoring of every attendance of every patient at their place of treatment, and identification of non-attenders and of problems encountered by clinic staff.** Non-attenders were followed up and motivated to return to their clinics. Whenever possible the clinic staff were encouraged to solve patient problems themselves, using community contacts and networks for tracing patients.
* **Establishing systems for ensuring drug supplies to clinics, and for transport of sputum specimens from clinics to laboratories, and results back to clinics.** The research nurse performed these functions herself whilst investigations and

discussions with hospital management sought to find methods for their routine implementation.

A policy was set that diagnosis would focus on bacteriology, and that treatment would use standardised treatment regimens, and that all patients would be provided with a supporter. The supporter system could not be set up only for the intervention patients, since it was considered unethical to deny all patients the widely accepted DOTS strategy.

15.7 Ethical issues

The study proposals were agreed to by Tintswalo managers, Gazankulu health authorities, and the University of the Witwatersrand Committee for Research on Human Subjects, whose clearance certificate is in appendix B3.

15.8 Analysis

Univariate and bivariate analysis was performed using chi-square tests and probability values derived from the Epistat programme of EpiInfo version 6.04 (Centers for Disease Control and Prevention,USA and World Health Organisation, 1996).

Multivariate analysis used the statistical package Stata (Stata statistical software 1997: release 5.0, College Statistics, TX: Stata corp.)

The data was tested for any design effect that sampling clinics might have had on results of individual patients. (Stata Survey commands. Stata Reference Manual Release 5, Volume 3, 381-439.)

CHAPTER 16

RESULTS OF INTERVENTION STUDY

This chapter includes:

- *Admission numbers*
- *Patient characteristics*
- *Disease characteristics*
- *Summary of key patient and disease variables*
- *Diagnosis*
- *Management*
  - *duration of hospital stay*
  - *treatment groups*
  - *supporters*
  - *bacteriological monitoring*
  - *treatment adherence*
- *Outcomes*
  - *distribution*
  - *comparison with outcomes of record review study (1992-1994)*
  - *relationship of outcomes to a number of variables*
  - *multivariate logistic regression*

Results of the intervention study to be presented in this chapter are those of patients admitted from the 1st July 1994 until 31st January 1996. The total tuberculosis admissions for the four-and-a-half-year period are the sum of patients studied in the record review (chapter 13), and this intervention study.

16.1 Admission numbers

There were 414 patients admitted to the tuberculosis unit for treatment during the 19 month period July 1994 to January 1996. The annual admissions for tuberculosis for the years 1992 to 1995 are shown in table 21 which also shows the total hospital admissions and the proportion of admissions for tuberculosis for each of the 4 years.

TABLE 21: TOTAL ADMISSIONS AND TUBERCULOSIS ADMISSIONS, TINTSWALO HOSPITAL 1992-1995

Year	Total Admissions (all causes)*	Tuberculosis Admissions	Percentage Admissions for Tuberculosis
1992	6303	248	3.9
1993	7708	186	2.4
1994	9793	205	2.1
1995	7699	268	3.4
Total	31 503	907	2.9

*Total admission figures may not be completely accurate.
Figures for the month of January 1996 (n=19) are not included.

Annual admissions over the 4 year period, and the mean per month are shown in figure 9.

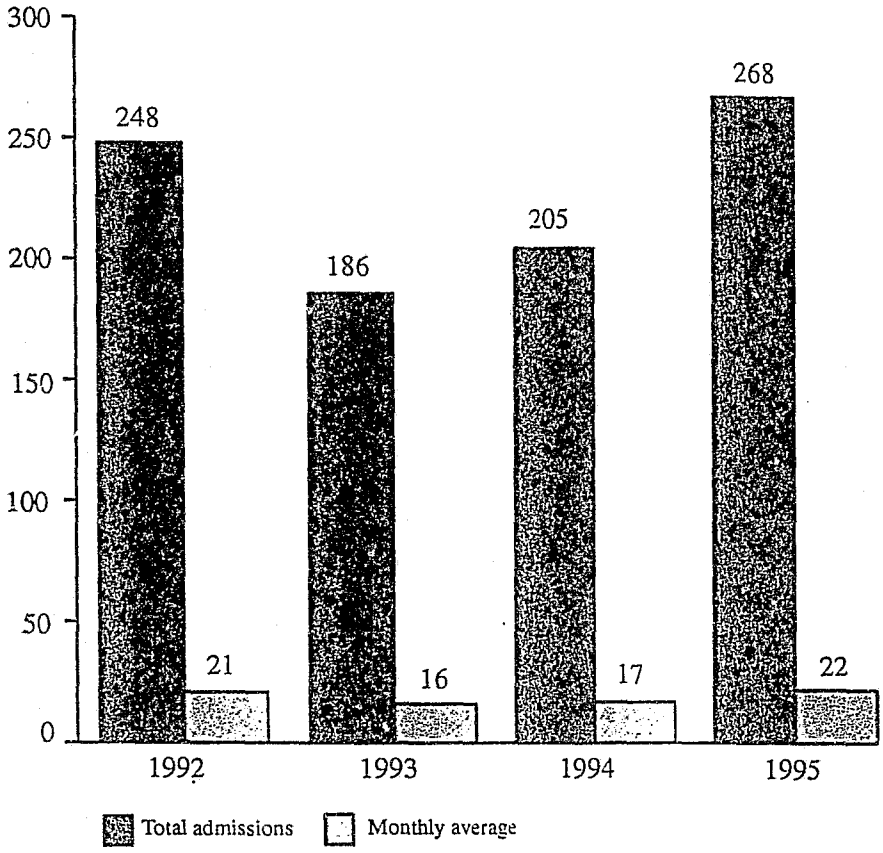


Figure 9: Monthly admissions for tuberculosis to Tintswalo Hospital for the period 1992 to 1995

16.2 Patient characteristics

16.2.1 Sex:

There were 292 male patients (71%) and 122 females (29%) in the 1994-1996 period.

16.2.2 Age:

The age distribution is shown in table 22, which demonstrates that 342 patients (83%) were between 15 and 59 years of age.

TABLE 22: AGE DISTRIBUTION OF PATIENTS (1994-1996)

Age category in years	n	%
0-5	23	6
6-14	23	6
15-29	89	21
30-59	230	56
60+	49	12
Total	414	101

The relationship between age and sex is shown in table 23.

TABLE 23: AGE AND SEX (1994-1996)

Age Group (years)	Females	Males	Total
0-5	10 (43%)	13 (57%)	23 (6%)
6-14	13 (57%)	10 (43%)	23 (6%)
15-29	41 (46%)	48 (54%)	89 (21%)
30-59	45 (20%)	185 (80%)	230 (56%)
60+	13 (27%)	36 (73%)	49 (12%)
Total	122 (29%)	292 (71%)	414 (100%)

Half of the children (under 15 years of age) were female, while 73% of those over 30 years of age were male. This difference was significant ($X^2=10.47$; df1; $p=0.001$).

16.2.3 Distance from patients' villages to hospital:

Distances from patients' villages to Tintswalo hospital were categorised as in table 24, in which the numbers and proportions of patients who lived within and outside the district boundaries is shown.

TABLE 24: DISTANCE ROM TINTSWALO HOSPITAL (1994-1996)

	Distance from patients' villages to hospital				TOTAL
	0-9 kms	10-25 kms	26-49 kms	50+ kms	
Within District	144 (44%)	108 (33%)	75 (23%)	0	327 (79%)
Outside District	0	9 (10%)	51 (59%)	27 (31%)	87 (21%)
Total	144 (35%)	117 (28%)	126 (30%)	27 (7%)	414 (100%)

Sixty five percent of all patients lived more than 9 kilometers from the hospital, and 37% more than 25 kms. For patients living **within the district**, 44% were within 9 kilometers, and 23% (43) more than 26 kilometers (to a maximum of 44 kilometers). For patients living **outside the district**, all lived more than 9 kilometers, 90% more than 26 kilometers, and 31% more than 50 kilometers from the hospital.

There were no differences in age and sex distributions between the distance categories. The relevant tables of data are in Appendices A4 and A5.

16.3 Disease characteristics

16.3.1 Type of disease:

Most patients, 332 or 80% of the total, had pulmonary tuberculosis, 31 (7%) had pleural effusions, 29 (8%) primary disease, 11 (3%) cervical adenitis, and 5 (1%) bone and joint TB. There were 2 cases each of abdominal TB and tuberculous meningitis, and one case each of miliary and renal disease.

16.3.2 Previous admissions:

Sixty three patients (15%) were recorded in their notes as being readmissions. Treatment outcomes of these previous admissions were as follows: cured 4 (6%), completed 23 (37%), interrupted 25 (40%), and failed 11 (17%). The remainder, 351 patients or 85% of the total, were recorded as new patients.

Of the 332 cases of pulmonary tuberculosis, 275 (83%) were recorded as new cases and 57 (17%) as "retreatment" cases. Patients who lived more than 9 kilometres from the hospital were more likely to have had a previous episode of tuberculosis ($X^2=3.9$; df1; $p=0.04$). The table of results is in Appendix A6.

16.3.3 Known readmissions within the study period:

Thirty seven patients, 5% of the 414 admissions, were readmitted during the period. Their characteristics will be analysed and discussed on page 204, after the results on treatment outcomes are presented.

16.3.4 Drug resistance:

Fifteen patients (5% of the pulmonary disease patients) had documented multi-drug resistance (MDR). A further 6 had resistance to isoniazid, one of these to streptomycin as well. A brief analysis of the features of this group of MDR patients on their admission showed the following:

> All 15 patients were adults, 6 between 15 and 29 years of age, 6 between 30 and 59, and 3 over 60. There were 12 males and 3 females. Seven had documented previous admissions in the period, the outcomes of which were "completed" treatment (4), cured (2) and failed (1). All the completing patients had been given two or three months supply of drugs to take unsupported at home. Eight patients had no documented admission at Tintswalo since 1992.

16.3.5 HIV status:

Results of HIV-infection were available for only 225 of the 414 patients (54%). The reasons for not testing the other 45% were unknown, and made it impossible to calculate an HIV-infected rate for all patients.

Eighty four percent of those tested were adults between 15 and 59 years of age. Three quarters were male.

In the untested group 33% were outside the 15 to 59 year age group (18% under 15 years and 15 % 60 or more), and 69% were males.

A larger proportion of smear positive cases were tested (70%) compared with 49% of other

patients, and more cases of pulmonary disease were tested (89%), compared with 72% of the others.

Of the 225 tested, 24 (11%) were positive. The age range for positive patients was 18 to 51 years, with mode of 35 years. Forty two percent were under 30 years of age. If the assumption were to be made that all unknown results were negative, the rate would be 6%. However the assumption is not entirely reasonable.

16.4 Summary of key patient and disease variables

Patient characteristics over the 4 years of the study, 1992-1995 (with January 1996) are shown in table 25 (overleaf).

TABLE 25: SUMMARY OF PATIENT AND DISEASE FEATURES, 1992-96 ADMISSIONS

	1992-94 n=514*	1994-96 n=414	Total n=928	Total %
	n (%)	n (%)		
Age 0-5	44 (9%)	23 (6%)	67	7
6-14	35 (7%)	23 (6%)	58	6
15-29	103 (20%)	89 (21%)	192	21
30-59	233 (45%)	230 (56%)	463	50
60+	98 (19%)	49 (12%)	147	16
Sex				
Female	170 (33%)	122 (29%)	292	31
Male	344 (67%)	292 (71%)	636	69
Distance (kms)				
0-9	182 (36%)	144 (35%)	326	35
10-25	213 (42%)	117 (28%)	330	36
26-49	77 (15%)	126 (30%)	203	22
50+	39 (8%)	27 (7%)	66	7
Previous TB				
Yes	82 (16%)	63 (15%)	145	16
No	430 (84%)	351 (85%)	781	84
Disease type				
Pulmonary	476 (93%)	332 (80%)	808	87
Primary	0	29 (7%)	29	3
Extrapulmonary	37 (7%)	53 (13%)	90	10

* For all except sex, data is missing for between 1 and 3 patients for the 1992-1994 data set.

16.5 Diagnosis

The results of sputum microscopy and culture tests done on the 332 patients with pulmonary tuberculosis are shown in table 26. [The numbers of tests done per patient were not recorded.]

TABLE 26: BACTERIOLOGICAL RESULTS OF PATIENTS WITH PULMONARY DISEASE, 1994-1996

Smear result	Culture positive	Culture negative	Culture unknown	Total
Positive	142 (66%)	1	72 (33%)	215 (65%)
Negative	60 (54%)	36 (32%)	15 (14%)	111 (33%)
Unknown	0	0	6 (100%)	6 (2%)
Total	202 (61%)	37 (11%)	93 (28%)	332 (100%)

The bacteriological coverage of the 332 patients with pulmonary disease was 94%, with 215 patients having smear and 96 culture results. Two hundred and fifteen patients were smear positive, and 60 were smear negative, culture positive, representing 275 patients (83%) with proven disease.

There were 36 who were smear negative and culture negative (11%), and a further 6% who were either smear negative, culture unknown (6 patients), or who had no tests recorded (6 patients).

There were thus 57 patients (17% of all) diagnosed and put onto treatment being smear negative and culture negative, or with no results.

16.6 Management

16.6 Management

16.6.1 Duration of hospitalisation:

Admission and discharge dates were available for all except 19 of the 414 patients (5%). Of the 395 with documented dates, 52 (13%) were not admitted to the ward. Those not admitted were more commonly under the age of 15 years (X^2=12.5; df1; p=0.0003), and had primary disease.

In figure 10 are the distribution of admission periods, including those not admitted.

Of the 343 admitted, the mean period was 30 days, median 18 days, and mode 15. For patients who lived within the district, the median was 18 days, for those from outside the district the median was 16½ days. One third were in-patients for 4 weeks or more.

Of those 130 patients admitted for more than one month, 26 (20%) were retreatment patients, the majority of whom had to spend two months in the ward to receive daily streptomycin.

The relationship between admission period and treatment outcome will be considered in the outcome section of this chapter, page 206.

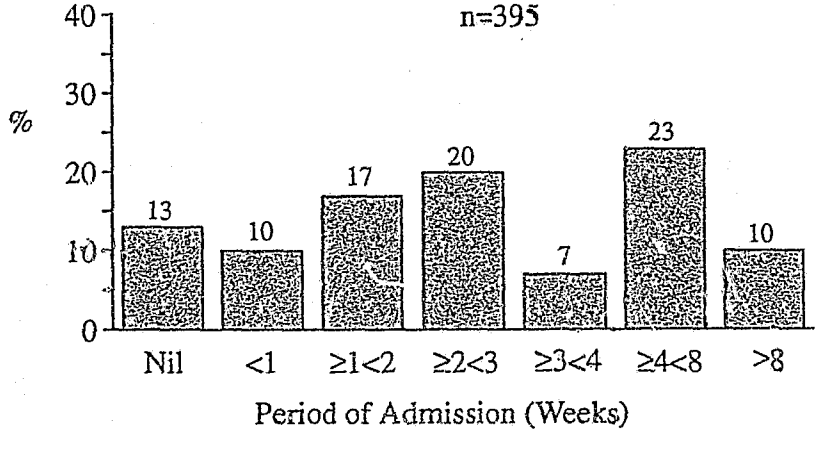


Figure 10: Distribution of hospital admission periods

16.6.2 Treatment groups:

Patients admitted during this period received treatment according to the groups defined in the methods. (page 163) The distribution of treatment groups is shown in table 27.

TABLE 27: NUMBERS AND PROPORTIONS OF PATIENTS IN DIFFERENT TREATMENT GROUPS, 1994-1996

Treatment Group	Clinic	n	%
INTERVENTION CLINICS	Buffelshoek	13	3
	Cottondale	21	5
	Ka.avukani	33	8
	Islington	12	2
	Thulamahashe	36	8
	Zoeknog	15	4
TOTAL TREATMENT CLINICS		130	32
TINTSWALO HOSPITAL	Control clinics	73	18
	Nearest facility	113	28
	Outside district	84	21
	Treatment clinic cases attending hospital	3	1
TOTAL TINTSWALO HOSPITAL		273	68
GRAND TOTAL		403 *	100

* excludes 11 patients transferred to other districts

Exceptions to attendance at allocated treatment places (Contamination of study groups):

There were 7 patients who attended a facility different to that expected according to the study allocations for their treatment.

Three treatment clinic patients attended hospital:

Three patients referred to district intervention clinics, attended Tintswalo hospital. For all three there were logical reasons for hospital attendance. One was a child whose mother worked at Hoedspruit, some 30 kilometers north of the hospital, another a child whose mother chose to attend the hospital, only slightly further way, and the third was a sick woman who was asked for clinical reasons to attend the hospital. She died during the treatment period.

Four patients allocated to control clinics attended a treatment clinic:

Four patients lived in Rolle which was very close to another village, Thulamahashe, served by an intervention clinic (actually a health centre). They were due to attend the hospital, but being closer to Thulamahase, they chose to attend that service.

No patients allocated to attend hospital requested treatment from a clinic.

A small number of intervention clinic patients attended the hospital once or twice during their treatment, either because the ward doctor asked them to return for some clinical reason, or for reasons of their own. Eleven patients, transferred to other health services outside the district, have been excluded from the figures. [These transfers will be discussed later.]

A comparison of figures for patients per treatment group with numbers expected from the 1992/93 study, and upon which the randomisation was based (as described on page 162 of the method section) show that numbers that could have been expected over a 18 month period were 93, 74 and 66 respectively for "treatment" and "control" clinic and "hospital" patients, while the actual patient numbers were 130, 73 and 113 respectively. These figures did, however, include 20 patients in January 1996, part of a nineteenth month. There were no significant differences in age and sex distribution of patients attending different treatment places. (Appendices A7 and A8)

The design effect of measuring selected variables in patients who were "clustered" according to sampled clinics was 0.44 (95% confidence levels 0.74,0.81). With this level of less than one, there was no measured clustering effect. Variables included were the clinics, patients' sex, ages, and whether or not patients had a treatment supporter, their knowledge and beliefs about tuberculosis, and their educational status. The last three variables were measured in the interview study to be described in chapter 18.

16.6.3 Supporters:

Three hundred and eighty eight patients received follow-up treatment in the community in the district. This number excludes 11 patients transferred out of the district and 15 patients who died in hospital. Three hundred and sixteen patients (81% of 388) had supporters organised to administer their DOTS, while 72 (19%) were unsupported. The distribution of supported patients per treatment groups is shown in table 28.

TABLE 28: DISTRIBUTION OF SUPPORTERS IN PATIENTS IN DIFFERENT TREATMENT GROUPS

	Supported	Not supported	Total
Intervention Clinics	123 (98%)	2 (2%)	125
Control Clinics	65 (92%)	6 (8%)	71
Hospital	91 (81%)	22 (19%)	113
Total in District	**279 (90%)**	**30 (10%)**	**309 80%**
Out of District	37 (47%)	42 (53%)	79 20%
Grand Total	**316 (81%)**	**72 (19%)**	**388 * 100%**

* 388 excludes 11 patients transferred, and 15 who died before suppporters could be organised

* Only 29 of 309 patients (9%) living in the district did not have supporters, while 42 of the 79 (53%) from outside the district did not. This difference was significant. (X^2=78.4; df1; p=0.000000).

* There were significantly more supported patients in the intervention group than in the other two groups in the district. (X^2=15.7; df1; p=0.00007)

* Those in the hospital group were less likely to be supported compared with all others (X^2=19.3; df1; p=0.00001)

* Significantly more intervention clinic patients were supported than those in the control clinic group. (Fisher's exact test p=0.027).

There was no difference in age groups of patients who were and were not supported, when comparing children under 16 years (X^2=3.1; df1; p=0.076), those 16 to 59 years (X^2=0.89; df1; p=0.34), and those 60 years and over (X^2=0.26; df1; p=0.61). Nor were there differences between the sexes (X^2=0.15; df1; p=0.7). (Supported patients with age and sex are in Appendices A9 and A10 respectively)

There was a similar proportion of new and retreatment patients who had supporters (77% and 74% respectively). The difference was not significant (X^2=0.38; df1; p=0.54). (The table of these results is in Appendix A11.)

Figure 11 shows the categories of supporters. They were selected for their willingness to participate, their ability to read and write (at least enough to place daily ticks on patients' cards in the correct places), and for their acceptability to patients. They also had to be accessible to patients, so that daily visits were not burdensome and time-consuming. The most common supporter category was the shopkeeper. These were either owners or managers of local stores in villages, and the nearest place from which basic commodities could be purchased. Second were individual family members of patients.

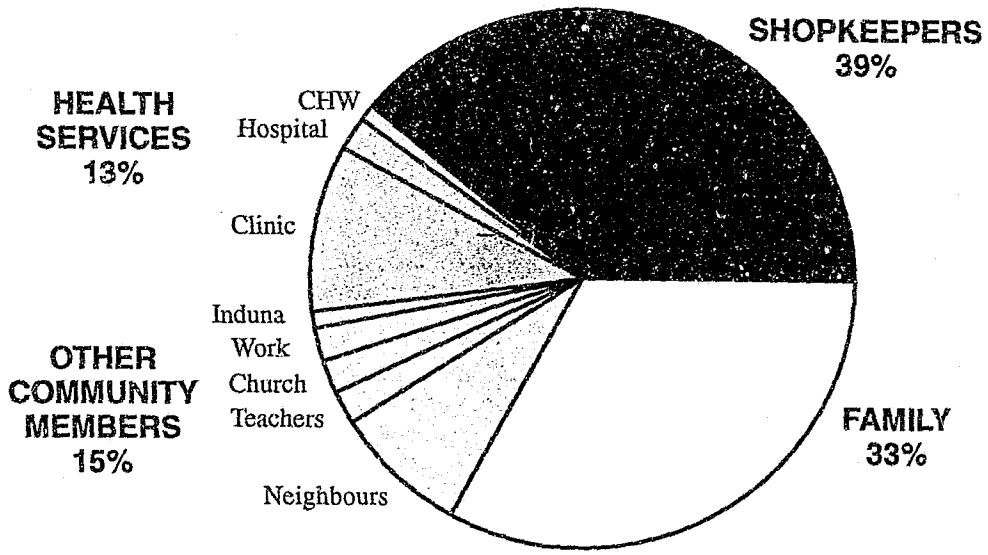


Figure 11: Categories of patient supporters

Nearly three quarters of supporters were in these two categories. Treatment clinic patients in the district were supported by a significantly higher proportion of clinic staff (19% compared with 9% of control clinic and 1% of hospital patients) (X^2=15.5; df1; p=0.00008), while a greater, but not significant proportion from outside the district had family supporters than those living in the district (43% compared with 32%) (X^2=1.93; df1; p=0.16) (Supporter category and treatment group are shown in Appendix A12.)

16.6.4 Bacteriological monitoring during treatment:

Table 29 shows the numbers and proportions of patients who had sputum microscopy performed during treatment, with a breakdown of tests and results for different treatment places, and for patient categories.

TABLE 29: BACTERIOLOGICAL MONITORING OF PATIENTS WITH PULMONARY DISEASE, WITH TREATMENT GROUPS AND CATEGORIES

Treatment Place/ Category	Total no. of cases	2 months smears performed	2 month smear positive	5-6 months smears performed	5-6 month smear positive
All	332	181 (55%)	25 (14% of 181)	101 (30%)	9 (9% of 101)
Intervention Clinic	103	54 (52%)	6 (11% of 54)	36 (35%)	4 (11% of 37)
Hospital*	229	127 (55%)	19 (15% of 127)	60 (26%)	5 (8% of 60)
New	275	148 (54%)	22 (15% of 148)	78 (28%)	7 (9% of 78)
Retreatment	57	33 (58%)	3 (9% of 33)	18 (32%)	2 (11% of 18)

* hospital includes "control clinic", hospital and "outside district" patients

At 2 months:

One hundred and eighty one patients (55% of 332 with pulmonary disease) had sputum microscopy tests after two months of treatment. Eighty six percent of these were negative. The proportion tested and the results were similar for clinic-treated and hospital-treated patients, and for new and retreatment patients.

At 5-6 months:

Only 30% of all patients were tested at 5 or 6 months, with a marginally, but not statistically significantly higher percentage of clinic-treated patients being tested ($X^2=2.64$; df1; $p=0.1$). Nine remained positive after 5-6 months of treatment, and thus were classified as failed outcomes. [In addition 7 patients were culture positive at the end of their treatment, so were also classified as "failed". See under treatment outcomes, page 194]

The proportions of new and retreatment patients tested, and their results, were similar.

16.6.5 Treatment adherence:

Urine metabolite measure:

Eighty nine patients were tested for isoniazid metabolites in the urine, (six having two tests each). No patient refused to have a specimen tested. Fifty tests (53% of all done) were performed at Tintswalo hospital, 38 at patients' homes and 7 at clinics. Fifty six tests (59%) were done during the second month of treatment, 15 (16%) during the third month, 10 (11%) during the fourth and 14 (15%) during the fifth and sixth months.

Eighty four tested positive (94%), and 5 negative. All five patients who tested negative admitted that they were not taking drugs at the time of the tests. Three had been tested at home, one each at the hospital and clinic.

Clinic or hospital attendance:

Patient attendances at clinics or at the hospital will be reported with treatment outcomes in the next section of this chapter.

16.7 Treatment Outcomes

16.7.1 Distribution of outcomes:

Treatment outcomes according to standard criteria are shown in table 30. The outcomes for patients in the earlier 1992-94 period are included for comparison.

TABLE 30 TREATMENT OUTCOMES, ALL PATIENTS, 1992-1996

Outcomes	1992-94		1994-96	
	n	%	n	%
Cured	0	0	41	10
Completed	307	60	261	63
Successful	307	60	302	73
Interrupted	154	30	62	15
Died	44	9	23	6
Failed	-	-	16	4
Transferred	9	2	11	3
Total	514	101 *	414	101 *

* percentages rounded

The outcomes of all new smear positive patients are shown in table 31. Results are very similar to the total group of patients.

TABLE 31 TREATMENT OUTCOMES, NEW SMEAR POSITIVE PATIENTS, 1992-1996

Outcomes	1992-94 Patients		1994-96 Patients	
	n	%	n	%
Cured	-	-	31	17
Completed	139	67	104	56
SUCCESSFUL	139	67	135	73
Interrupted	52	25	26	14
Died	16	8	9	5
Failed	-	-	9	5
Transferred	2	1	5	3
Total	209	101*	184	100

*percentages rounded

There is a significant difference in the 73% successful outcomes of this period and the 60% (best estimate) calculated for the 1992-1994 period.(X^2=20.3; df1; p=0.000006). The difference remains significant for new smear positive cases.(X^2=6.2; df1; p=0.007)

Cured and Completed treatment:

The overall 73% cured and completed rate is an improvement on the 60% measured for the 1992-1994 study patients. Only 41 (14%) of 302 patients with successful outcomes were in the "cured" category with measured conversion of smear positive to smear negative sputa. Among smear positive new cases, there were 31 cured patients (17% of all, and 23% of all successful outcomes).

Failed treatment:

Bacteriological monitoring of sputa at the end of treatment identified 9 smear positive, and 7 smear negative, culture positive patients. The records indicate that culture tests were performed on these 7 because failure was suspected on clinical grounds. Thus when the

smears were negative, culture tests were done in addition. This was not routine for all cases.

Transfers:

A small number of patients were transferred out of the district. If they are removed from the denominator, the percentage of patients completing treatment is 75%. The 11 patients transferred (which process involved giving them a transfer form to give to the staff of the nearest health facility) were referred to distant cities (two to Johannesburg, one to Pretoria), to a tertiary hospital for management of an associated leukaemia, a mine hospital in another province (Free State), towns in Mpumalanga and Northern Provinces (Graskop, Hoedspruit, Tzaneen, Phalaborwa), the neighbouring district hospital (Mapulaneng), and to the Barberton prison health service. At least 7 of these patients were moving away to seek or continue work. Eight were males, 10 were adults. The results of patient attendance and of outcome associations will exclude those 11 patients transferred.

Deaths:

The 23 deaths were recorded in the Tintswalo hospital records and in the tuberculosis register. Some of these had death certificates.

Interrupted treatment:

The rate of interruptors in the later period was half that in the earlier period, decreasing from 30% to 15%.

Results of specific follow-up by the research team of the 35 interruptors who had given addresses in the district are shown in table 32.

TABLE 32: REASONS FOR INTERRUPTING TREATMENT

Reason for interruption	TREATMENT PLACE			Total
	Intervention Clinics	Control Clinics	Hospital	
"Moved away"	5	1	7	13 (37%)
Not found	2	3	6	11 (31%)
Refused treatment	7	-	2	9 (26%)
No money	-	2	-	2 (6%)
Total	14	6	15	35 (100%)

Thirteen of the 35 interruptors (37%) had **moved out** of the area. According to relatives staying at the addresses given by the patients, nine had gone to a town in the Northern Province or Mpumalanga, three to Johannesburg or Pretoria, and one to another area. Two were females who had moved to one of the local sawmill towns in Mpumalanga with their husbands who worked there. Eleven patients **could not be found.** A minimum of three visits to the given addresses of each of these patients failed to identify the patients' whereabouts. These patients may also have been out of the district. Only two of the 14 interruptors on treatment at intervention clinics were in this "not found" category, compared with larger proportions (50% and 40%) in control clinic and hospital patients respectively. Nine patients had **refused treatment.** One was female, eight were males, and one was a child whose mother refused treatment. Several of these patients were described by the health workers who visited them as aggressive, at least two were using dagga. One patient's reason was **lack of money** to reach hospital. He lived a short taxi ride away.

Treatment outcomes of MDR patients:

Outcomes of the 15 patients with MDR were as follows:

seven completed, two cured, three interrupted, two failed and one still on trea ·nt at the end of this study. Only four had had bacteriological testing at the end of treatment.

Outcomes in different treatment groups

Treatment outcomes for patients in different groups are shown in table 33.

TABLE 33: TREATMENT OUTCOMES AND TREATMENT GROUPS: ALL PATIENTS

Treatment place	Cured	Compl.	Interrpt.	Died	Failed	Total
Treatment clinics (within district)	17 (13%)	86 (66%)	14 (11%)	7 (5%)	6 (5%)	130 32%
Control clinics (within district)	7 (10%)	53 (73%)	6 (8%)	5 (7%)	2 (3%)	73 18%
Tintswalo Hospital (within district patients)	15 (13%)	75 (65%)	15 (13%)	6 (5%)	5 (4%)	116 29%
Total "in district" patients	39 (12%)	214(67%)	35 (11%)	18(6%)	13(4%)	319 79%
Tintswalo Hospital ("outside district" patients)	2 (2%)	47 (56%)	27 (32%)	5(6%)	3 (4%)	84 21%
Grand Total	41 (10%)	261(65%)	62 (15%)	23(6%)	16(4%)	403* 100%

* excludes 11 patients transferred

Outcomes within the district:

There were no differences in outcomes for patients in different treatment groups within the district. This applied to the intervention group compared with rest (X^2=0.00; df1; p=0.97), for the control group compared with the rest (X^2=0.48; df1; p=0.49), and for the hospital group compared with the rest (X^2=0.51; df1; p=0.47)

Outcomes outside the district:

A significantly lower proportion of patients from outside the district successfully completed treatment compared with those from within (X^2=15.11; df1; p=0.0001).

For new smear positive patients, there were similarly no differences between groups in the district patients, but significantly better outcomes for all district cases compared with outside the district (X^2=12.4; df1; p=0.0004). (Table 34).

TABLE 34: TREATMENT OUTCOMES AND TREATMENT GROUPS, NEW SMEAR POSITIVE PATIENTS

Treatment place	Cured	Complt.	Interruptd	Died	Failed	Total
Treatment clinic (within district)	12 (20%)	37 (62%)	6 (10%)	2 (3%)	3 (5%)	60 (36%)
Control clinics (within district)	5 (20%)	17 (68%)	1 (4%)	1 (4%)	1 (4%)	25 (14%)
Tintswalo hospital	13 (21%)	34 (56%)	7 (11%)	3(5%)	4 (7%)	61 (34%)
Total "in district" patien	**30(21%)**	**88 (60%)**	**14 (10%)**	**6 (4%)**	**8 (5%)**	**146(82%)**
Tintswalo Hospital ("outside district" patients)	**1 (3%)**	**16 (48%)**	**12 (36%)**	**3 (9%)**	**1 (3%)**	**33 (18%)**
Grand Total	31 (17%)	104 (58%)	26 (15%)	9 (5%)	9 (5%)	179

16.7.2 Comparison with outcomes of the record review study of 1992-1994:

If patients admitted during the 1992-94 period are categorised according to the treatment places allocated in the 1994-96 intervention study, it is possible to measure any change in treatment outcomes for the 2 periods according to geographic location of the patients. (Table 35) Of patients in the district, 63% had successful outcomes, with no significant differences in outcomes for different treatment localities. The control clinic rate of 59% was not significantly lower ($X^2=1.35$; df1; $p=0.24$). For those living outside the district, the completion rates were 52% overall, significantly lower then those of patients living within the district.($X^2=17.0$; df1; $p=0.00003$) Successful treatment proportions of these outside district patients decreased with increasing distance categories from Tintswalo hospital (62%,53% and 41%). The trend was not quite statistically significant.(X^2 for linear trend=3.55; $p=0.059$) Those who lived 50 kilometres or more from the hospital were less likely to complete their treatment.($X^2=7.7$; df1; $p=0.005$)

The proportion of patients with successful outcomes after the intervention (58%) was no different from that before the intervention (52%).($X^2=0.75$; df1; $p=0.38$).

TABLE 35: TREATMENT OUTCOMES FOR ALL 1992-94 PATIENTS, CATEGORISED BY INTERVENTION STUDY GROUPS

Place for treatment	Completed	Interrupted	Died	Total
Treatment clinics	101 (65%)	40 (26%)	14 (9%)	155 (31%)
Control clinics	72 (59%)	40 (33%)	10 (8%)	122 (18%)
Hospital group	71 (65%)	30 (28%)	8 (7%)	109 (29%)
Total "in-district" patients	**244 (63%)**	**110 (28%)**	**32 (8%)**	**386 (78% of all)**
Outside-district 10-25 kms distant	26 (62%)	14 (33%)	2 (5%)	42 (8%)
Outside-district 26-49 kms distant	20 (53%)	12 (32%)	6 (16%)	38 (8%)
Outside-district 50+kms distant	15 (41%)	18 (49%)	4 (11%)	37 (7%)
Total "outside-district" patients	61 (52%)	44 (38%)	12 (10%)	117 (23% of all)
Grand Total	305 (61%)	154(31%)	44 (9%)	503 * 101%

*excludes 9 transferred patients and 2 for whom data was missing

Smear positive patients:

The results were similar for new smear positive patients, with no differences in completed rates for patients in different treatment groups within the district (70%, 68% and 69%). The 69% success rate in the district cases was significantly better than the 55% of patients from outside the district.($X^2=6.6$; df1; $p=0.009$) Distances of 50 kilometers and more were significantly negatively related to successful treatment outcomes.($X^2=4.3$; df1; $p=0.03$) The smear positive results are detailed in Appendix A13.

The comparison of the two study periods is facilitated by table 36 in which the percentage outcomes for the 2 periods is shown.

TABLE 36: TREATMENT OUTCOMES PER TREATMENT GROUP, TWO STUDY PERIODS COMPARED

Outcome	TRCL 94-96	TRCL 92-94	COCL 94-96	COCL 92-94	HOSP 94-96	HOSP 92-94	IN-DS Total 94-96	IN-DS Total 92-94	OS 94-96	OS 92-94
No. cases	130	155	73	122	116	109	319	386	84	117
% Compl	79	65	82	59	78	65	79	63	58	52
% Interr	11	26	8	33	13	28	11	28	32	38
% Died	5	9	7	8	5	7	6	8	6	10
% Failed	5	-	3	-	4	-	4	-	4	-

Codes:
Treatment place: TRCL= Treatment clinic, COCL=Control clinic, HOSP= Hospital,
IN-DS =In district, OS= Outside district

This table demonstrates that:

i) completed outcomes for "in-district" patients are similar for different treatment places within each study period

ii) completed outcomes in the 94-96 intervention period are better than in the 92-94 period

iii) the completed outcome rates in the intervention clinics are not greater nor less than those in the control and hospital groups, despite the new system at these intervention clinics, and despite specific research interventions targeted at these

iv) interruption rates rise and fall with changes in completion rates, the death rate being more or less constant

v) completion rates in patients from outside the district are significantly less than for "in-district" patients, and are similar in the 2 study periods.

16.7.3 Relationship between treatment outcomes and other variables

Eleven patients transferred away from the responsibility of Tintswalo hospital and clinics have been excluded from the analysis unless otherwise stated. Thus the number of patients examined is 403. When the term "successful" treatment is used, it refers to the combined "completed" and "cured" outcome categories.

Sex and outcome:

There was no association between sex and successful outcomes. This applied whether deaths were included ($X^2=1.47$; df1; $p=0.22$), or not ($X^2=2.6$; df1; $p= 0.11$).

Although the difference is not significant, new smear positive females appear to be more likely to complete treatment when successful treatment is compared with all other outcomes. ($X^2=2.9$; df1; $p=0.087$) When deaths are excluded, there was no difference. ($X^2=1.96$; df1; $p=0.16$) Tables showing results of all and of smear positive patients are to be found in Appendices A14 and A15.

When the 23 deaths were analysed by sex, more males died (15 or 61%) than females (8 or 39%). There was a slightly, but not significantly, higher proportion of all females that died (8 of 122 or 7%), compared with males (15 of 392, or 4%). ($X^2=0.33$; df1; $p=0.56$)

Age and outcome:

The association between outcomes and different age groups can be seen in table 37.

TABLE 37: TREATMENT OUTCOMES AND AGES: 1994-1996 study

Age group (years)	Cured and completed	Interrupted	Died	Failed	Total
0-14	36 (80%)	9 (20%)	0	0	45 (11%)
15-29	72 (86%)	11 (13%)	0	1 (1%)	84 (21%)
30-59	162 (72%)	35 (16%)	18 (8%)	10 (4%)	225 (56%)
60+	32 (65%)	7 (14%)	5 (10%)	5 (10%)	49 (12%)
Total	302 (75%)	62 (15%)	23 (6%)	16 (4%)	403 (100%)

Patients under the age of 30 years were more likely to have successful outcomes than those 30 years and more.($X^2=8.58$; df1; $p=0.003$). The significant relationship remained when those under 15 years were excluded.($X^2=8.5$; df1; $p=0.003$). Deaths occurred exclusively in those over 30 years of age. When deaths were excluded, there was no association between age and outcome.($X^2=2.15$; df1; $p=0.14$)

For new smear positive patients, there was a similar association between successful outcomes and age (x^2df1$=6.21$, $p=0.012$). Appendix A16 contains this data.

Previous treatment and outcomes:

Outcomes of patients recorded as having had previous treatment were compared with those of "new" patients. (Table 38)

TABLE 38: TREATMENT OUTCOMES FOR NEW AND RETREATMENT PATIENTS (1994-1996)

Treatment category	Cured and completed	Interrupted	Died	Failed	Total
New	264 (77%)	48 (14%)	18 (5%)	11 (3%)	341 (85%)
Re-treatment	38 (61%)	14 (23%)	5 (8%)	5 (8%)	62 (15%)
Total	302 (75%)	62 (15%)	23 (6%)	16 (4%)	403 * (100%)

Patients on their first course of treatment were more likely to have successful outcomes, than those who were being re-treated (X^2=7.25; df1; p=0.007). When deaths were excluded, the relationship remained (X^2=6.72; df1; p=0.009).

Outcomes and readmissions:

There were 37 patients readmitted within the study period, 17 readmitted during their first course of treatment and 20 having had a course of treatment in the past with various outcomes. At their **first admissions** (within the period July 1994 and January 1996), 13 were smear positive, and one had multi-drug resistant disease at the start of treatment. Treatment outcomes of these 20 were as follows: twelve interrupted (60%), five completed, one cured, and two failed. At the **second admission** of 18, 12 were smear positive, and four had MDR. Six completed treatment this time, four interrupted, for four the period of treatment had not yet elapsed, three failed, and one died. Five patients had a **third admission** in the period, 2 of whom completed treatment, and 3 of whom were still on their 8 months' retreatment course when this analysis was done.

Type of disease and outcome:

The outcomes of 4 categories of disease, pulmonary, primary, pleural effusions and other, were compared and are presented in table 39. Patients transferred elsewhere are not included in these figures: of the 11, 10 had pulmonary disease and one a pleural effusion.

TABLE 39: TREATMENT OUTCOMES AND DISEASE TYPE (1994-1996)

Disease type	Cured and completed	Interrupted	Died	Failed	Total
Pulmonary	241 (75%)	47 (15%)	19 (6%)	16 (5%)	323 (80%)
Primary	22 (76%)	7 (24%)	0	0	29 (7%)
Pleural effusion	23 (79%)	3 (10%)	3 (10%)	0	29 (7%)
All other	16 (73%)	5 (23%0	1 (5%)	0	22 (5%)
Total	302 (75%)	62 (15%)	23 (6%)	16 (4%)	403 * (100%)

There were no significant differences in successful and unsuccessful outcomes (X^2=0.28; df1; p=0.59), nor in deaths (Fishers exact test, p=0.52) between patients with pulmonary disease and other types.

HIV-infection and outcomes:

Outcomes and HIV status are shown in table 40.

TABLE 40: TREATMENT OUTCOMES AND HIV STATUS (1994-1996)

HIV status	Compl. & cured	Died	Failed	Interrupted	Total
Negative	157 (80%)	6 (3%)	11 (6%)	23 (12%)	197 (90%)
Positive	18 (78%)	4 (17%)	0	1 (4%)	23 (10%)
Total	175	10	11	24	220 *

* 225 patients were tested for HIV. 5 have been excluded, as they were transferred out of the district

There was no difference in HIV status for patients with successful outcomes compared with other outcomes. (Fisher exact test p=0.52) When deaths in HIV-positive patients were compared with HIV-negatives, there were significantly more deaths in the HIV-

infected group. (Fisher exact test p=0.01) [HIV-infection rates as recorded, are not an accurate reflection of prevalence]

Hospital admission period and outcome:

Being admitted to hospital was not related to a successful treatment outcome.(X^2=1.07; df1; p=0.3) Nor were different periods of admissions related to outcomes, either seven days (Fisher exact test p=0.20), nor 28 days.(X^2=1.99; df1; p=0.16) This data is in Appendices A17, A18, A19.

Supported treatment and outcome:

Outcomes of patients who had supported and unsupported treatment are compared in table 41. Patients who were supported were more likely to complete their treatment.(X^2=19; df1; p=0.0000)

TABLE 41: TREATMENT OUTCOMES AND SUPPORTED TREATMENT

Support	Completed	Interrupted	Died	Failed	Total
Yes	260 (82%)	37 (12%)	6 (2%)	13 (4%)	316 (83%)
No	42 (58%)	25 (35%)	2 (3%)*	3 (4%)	72 (17%)
Total	302 (78%)	62 (16%)	8 (2%)*	16 (4%)	388* (100%)

* excludes 11 transfers and 15 who died before discharge from hospital, thus did not have supporters.

For smear positive patients a significant difference remained with supported patients being more likely to complete, compared with all other outcomes.(X^2=12.9; df1; p=0.0003) (Appendix A20)

Supported treatment in different treatment groups:

The percentage of patients supported at different treatment places is shown in table 42.

TABLE 42: TREATMENT OUTCOMES AND TREATMENT GROUPS OF SUPPORTED PATIENTS

Treatment groups	Completed & cured		Interrupted		Died		Failed		Total sup-ported
	n	% supp	n	% supp	n	% supp	n	% supp	
Treatment clinics	103	100	12	86	2	29	6	100	123 98%
Control clinics	56	93	5	83	2	40	2	100	65 92%
Hospital	79	88	6	40	2	33	4	80	91 81%
Outside district	22	45	14	52	0	0	1	33	37 47%
Total	260		37		6		13		316 83%

All patients who successfully completed treatment at treatment clinics were supported, whereas less than half of those with successful outcomes in the outside district group were supported.

Sputum microscopy results at 2 months and outcome:

The proportion of cases of pulmonary disease who had sputum smear monitoring was described on page 191. This section analyses treatment outcomes of those who had positive and negative tests at two months.

Only 181 of 328 patients (55%) with pulmonary disease (332 excluding 8 transferred) had sputum tests after two months of treatment, 86% of which were negative. (Table 43)

TABLE 43: TREATMENT OUTCOMES AND TWO MONTH SMEAR MONITORING (SMEAR POSITIVE CASES)

Sputum result as 2 months	Completed & Cured	Interrupted	Failed	Total
Positive	19 (76%)	4 (16%)	2 (8%)	25 (19%)
Negative	128 (82%)	17 (10%)	11 (7%)	156 (86%)
Total	147 (81%)	21 (11%)	13 (7%)	181 (100%)

When results for successful and unsuccessful outcomes were compared, there was no difference in the proportions with negative 2 month tests.(Fisher exact test p=0.31)

* Of the 25 patients who tested positive at two months, 19 (76%) had a successful treatment outcome (16 completed and 3 cured). The ability of the monitoring test to predict poor outcomes was low (6/25 or 24%).
* Of the 156 who tested negative at two months, 128 (82%) had an ultimately successful outcome.

Since numbers of bacteriological conversions were small, no accurate assessment can be made of the predictive value of the two month test.

New and retreatment patients were analysed separately. Of 148 new smear positive cases 126 were smear negative at 2 months, with 108 of these (86%) went on to successful outcomes. Twenty two were positive at 2 months, of whom 17 (77%) completed treatment or were cured. Of 33 retreatment patients, 30 were negative at 2 months, with 20 of those (67%) success-fully completing treatment. Only 3 were positive, and 2 of these completed treatment.

Attendance at clinics or hospital:

An analysis of treatment outcomes (completed, interrupted and failed) is illustrated in table 44 which also shows treatment supporters for each treatment group.

TABLE 44: SUCCESSFUL OUTCOMES: ATTENDANCE AND SUPPORTERS PER TREATMENT GROUP

Treatment place	ATTENDANCE			
	Monthly thro'out	Monthly for first 2 months	2-3 monthly thro'out	Total
TREATMENT CLINICS	73 (71%)	19 (18%)	11 (11%)	103 (34%)
supporters	73 (100%)	19 (100%)	11 (100%)	103 (100%)
CONTROL CLINICS	29 (48%)	24 (40%)	7 (12%)	60 (20%)
supporters	28 (97%)	21 (88%)	7 (100%)	56 (93%)
HOSPITAL	47 (52%)	30 (33%)	13 (14%)	90 (30%)
supporters	42 (89%)	24 (80%)	13 (100%)	79 (88%)
OUTSIDE DISTRICT	18 (37%)	14 (29%)	17 (35%)	49 (16%)
supporters	8 (55%)	9 (64%)	5 (29%)	22 (45%)
TOTAL NO.	167 (55%)	87 (29%)	48 (16%)	302
Total supporters	151 (90%)	73 (84%)	36 (75%)	260 (86%)

The following are the essential features of results for patients who had **successful outcomes:**

Treatment clinic attendance and supported treatment:

71% of these patients attending treatment clinics did so on a monthly basis. Whatever the frequency of attendance the proportion of patients supported was 100% for these clinic patients.

Treatment group differences:

About half of those in each of the "control clinic" and "hospital" groups, and 37% of the "outside district" group attended the hospital for their regular visits on a monthly basis. A larger proportion of those attending treatment clinics attended monthly ($X^2=15.3$; df1; $p=0.00009$), those from within the district were significantly more likely to attend

monthly.(X^2=8.1; df1; p=0.004).

Supporters for "in" and "outside" district patients:

For patients living in the district, the proportion with supporters was high (86%, range 88-100%), whether patients attended monthly or less often. Those living outside the district were less supported, 45% of all, and only 29% for those who attended infrequently.

Attendance and supporters:

A smaller proportion of patients who attended less than monthly had supporters compared with more regular attenders.(X^2=5.8; df1; p=0.01).

Attendance and interrupted treatment:

The attendance patterns and supporters for the 37 patients who interrupted treatment were analysed. Although firm conclusions could not be drawn from the small numbers, patients in different treatment groups, as well as those "in" and "outside" the district, appeared to complete the initial two months of treatment in similar proportions.

Attendance of patients with failed outcomes:

Eleven of the 16 patients who failed treatment attended monthly (10 of the 11 were supported), three completed the first two months, then were irregular (two of the three were supported), and two were irregular throughout treatment, one being supported.

Distance from hospital and outcome:

For patients who travelled to Tintswalo hospital for their treatment, outcomes for different distance categories were compared. (Table 45) Those of the intervention group who attended a local clinic for whom distance was not a major factor were excluded.

TABLE 45: TREATMENT OUTCOMES AND DISTANCE FROM TINTSWALO HOSPITAL FOR ALL PATIENTS ATTENDING HOSPITAL

Distance to hospital (kms)	Completed & cured	Interrupted	Died	Failed	Total
0-9	95 (80%) 48%	14 (12%) 29%	6 (5%) 38%	4 (3%) 40%	119 44%
10-25	45 (76%) 23%	9 (15%) 19%	3 (5%) 19%	2 (3%) 20%	59 22%
26-49	45 (63%) 23%	17 (24%) 35%	5 (7%) 31%	4 (6%) 40%	71 26%
50+	14 (58%) 7%	8 (33%) 16%	2 (8%) 13%	0	24 9%
Total	199 (73%) 101%	48 (18%) 100%	16 (6%) 100%	10 (4%) 100%	273 * 100%

* excludes 11 transferred and 130 in intervention group

Significantly more patients who lived within 9 kilometers (X^2=5.1; df1; p=0.02), and within 25 kilometers (X^2=8.55; df1; p=0.0034) of the hospital had successful outcomes.

There was a significant decreasing trend of successful outcomes with increasing distance from the place of treatment. (X^2 for linear trend=8.5; p=0.0035) Patients in different distance categories were similar in terms of their age groups and sexes, and in whether they were new or retreatment patients. When only patients living in the district were considered, distance from the hospital for those who had to travel there for treatment, was not related to outcomes. Ninety five of the 150 patients who completed treatment lived within 9 kilometers of the hospital, whereas 14 of the 21 interruptors lived 10 or more kilometers distant. (X^2 0.09;df1;p=0.77) When unsuccessful treatment included interrupters, those who died and those who failed treatment, distance remained unrelated to outcomes. (X^2=0.04;df1;p=0.8)

Geographic clusters and outcome:

Geographic clusters in the study area with approximate sizes are depicted in figure 12 on page 213. Areas were arbitrarily defined using knowledge of the ethnic groupings of people and of transport routes. The proportion of patients in each treatment group for each area in the district is shown in table 46, and the treatment outcomes together with a number of variables already considered summarised in table 47 on page 214.

TABLE 46: PROPORTION OF PATIENTS PER TREATMENT GROUP PER GEOGRAPHIC CLUSTER WITHIN THE DISTRICT

Area	TREATMENT GROUP					
	Intervention Clinic		Control Clinic		Hospital	
	n	%	n	%	n	%
1	0	0	0	0	36	100
2	34	71	6	13	8	17
3	29	78	7	19	1	3
4	25	54	8	17	13	28
5	28	72	11	28	0	0
6	0	0	15	20	62	81
7	16	36	28	64	0	0
Total	132		75		120	

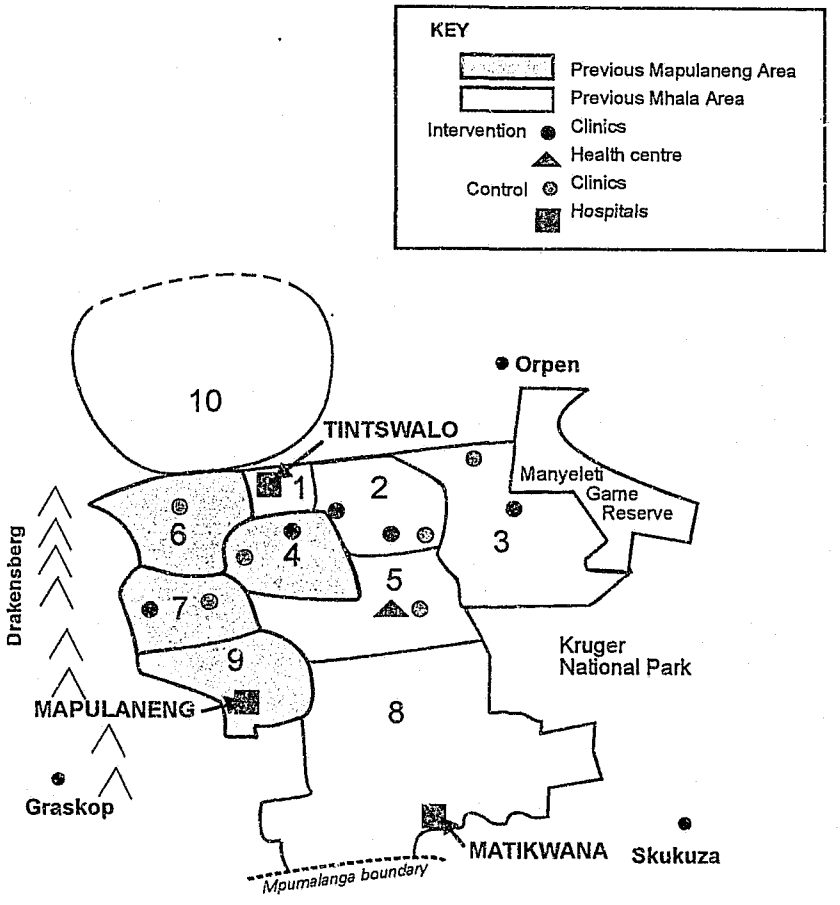


Figure 12: Ten arbitrarily defined geographic clusters in the Bushbuckridge subregion

TABLE 47: OUTCOME, DEMOGRAPHIC AND HEALTH SERVICE VARIABLES BY GEOGRAPHIC CLUSTERS

Area no.	n pts	Successful outcomes (%)	Interrupted outcomes (%)	% under 30 yrs	% Female	% 26+ kms distant from T. hospital	% positive HIV	% with support	% per treatment group *		
									TR n=132	CC n=75	H n=120
1	36	83	8	25	31	0	3	81	0	0	100
2	47	83	11	33	35	29	6	90	71	13	17
3	35	74	14	51	32	100	14	89	78	19	3
4	45	87	4	24	26	0	9	87	54	17	28
5	39	72	15	26	26	62	5	92	72	28	0
6	75	80	15	35	25	0	1	79	0	20	81
7	42	74	7	30	25	0	7	86	36	64	0
Total in dist.	**319**	**79**	**11**	**32**	**28**	**23**	**6**	**86**	**40**	**23**	**37**
8	17	59	28	28	33	56	17	33			
9	51	59	31	43	41	82	2	53			
10	16	56	33	17	17	94	6	22			
Total out of dist.	84	58	32	35	35	90	6	42			

* TR=treatment clinic group, CC=control clinic group, H=hospital group

Treatment outcomes: The proportion of successful treatment outcomes within the district was lowest in areas 3,5 and 7, all of which were further from Tintswalo hospital. The difference between the successful rates in these areas and all others was not significant (x^2=3.67; df1; p=0.055). Interrupted outcomes were significantly higher in areas 3,5 and 6 (x^2=3.89; df1; p=0.048). The other causes of unsuccessful outcomes were failed treatment (highest in areas 1 and 5) and deaths (highest in area 7).

When patients who attended intervention clinics were excluded, successful outcome rates were the same except in areas 2,3 and 4 where there were slight decreases (to 77%, 71%, 80% respectively)

Ages and sex: The proportion of young people (under 30 years of age) was significantly higher in areas 3 and 9 (X^2=9.66; df1; p=0.0018) Forty one percent of area 9 patients were females, more than in other areas (X^2=4.76; df1; p=0.029)

Distances: All patients in area 3 and most in 5 were over 25 kilometers away, while those from outside were ~ 1 further.

HIV: HIV-infection in those measured was significantly higher in areas 3 and 8 (X^2=12.99; df1; p=0.0003)

Supporters: Patients in most areas in the district had supporters, as stated before, but for those living outside the district boundaries the proportions were less.

The allocated place of treatment was not equally distributed among the 7 areas. The hospital group predominance was as expected for areas 1 and 6. Area 6 did not contain a treatment clinic.

16.7.4 Multivariate logistic regression analysis:

The relationship between treatment outcomes (dichotomised as "successful" or "unsuccessful") and a number of potential explanatory variables was examined by fitting a range of multiple regression models using the statistical package Stata, as described under methods in chapter 15. Successful outcome was defined as cured or completion of the course of treatment, while unsuccessful outcome was defined as death or interrupted or failed treatment. Two multivariate models were used in order to identify predictors of successful outcome of treatment. One model examined the determinants of successful outcome in patients who lived within the district, and included sex, age, the treatment group ("treatment" or "control" clinic or "hospital"), the presence or absence of a treatment supporter, distance from patients' homes to Tintswalo hospital, and whether or not patients had had previous treatment. Other variables, derived from results of the interviews on patients (to be described in chapter 17) included patients' educational levels, their beliefs in the cause of tuberculosis, their type of work, which health facility they attended when first sick, their household size and the number of children per household under five years of age. Varying the cutpoints for continuous independent variables did not alter the associations materially.

The second model examined the predictors of successful outcomes in patients who lived outside the district. Independent variables used in this analysis included age, sex, distance from home to hospital, supporter presence or absence, and new or retreatment patient categories.

Variables were omitted from the models if the change in residual model deviance on dropping the variables was not statistically significant.*

* D.Collett. Modelling binary data. Chapman and Hall. London 1991:62-67

For patients who lived in the district. explanatory variables found to be positively associated with succes ful outcomes were 1) having a treatment supporter, 2) the belief that spread from other pe .e with tuberculosis causes the disease, and 3) presenting as a new, rather than as a re-treatment patient, and 4) more than three years of formal education. These positive associations are shown in table 48.

TABLE 48: LOGISTIC REGRESSION ANALYSIS: SUCCESSFUL TREATMENT OUTCOME *

Variable	Odds ratio	SE	Z	p	95% CI
Supported treatment (vs not supported)	12.2	6.8	4.5	0.000	4.1, 36.2
Previous treatment) (vs first treatment)	0.17	0.08	-3.6	0.000	0.06, 0.45
Belief in environmental/lifestyle cause (vs belief in germs or spread)	0.33	1.5	-2.4	0.017	0.13, 0.82
Formal education for more than 3 years (vs less than 3 years formal education)	2.6	1.2	2.1	0.036	1.06, 6.35

* successful outcomes were patients who were "cured" and those who"completed" treatment

For patients who lived outside the district, none of the independent variables were significantly associated with successful outcomes. Small numbers may have been the reason for this.

CHAPTER 17

INTERVENTION STUDY RESULTS: DISCUSSION AND CONCLUSIONS

This chapter includes:

Discussion of

patients and their diseases

diagnosis

treatment outcomes and their determinants

Conclusions

17.1 The patients and their disease

Incidence and admission rates:

Annual admissions to Tintswalo hospital varied slightly over the 4 year period 1992 to 1995, with fewer admissions during 1993. As discussed in chapter 13 (the record review study), it is difficult to comment on admission rates or on tuberculosis incidence rates in this region. Districts were not defined, population figures were unknown, patients with disease consulted services outside their own district, the notification process was inefficient, and hospital utilisation was erratic due to periodic staff strikes which brought services to a virtual halt.

The mean number of annual admissions for tuberculosis to Tintswalo hospital over the 4 year period 1992 to 1995 was 227. Assuming an annual readmission rate of 10%-15%, the annual incidence during this period could be 200 per 250 000 (the approximate Tintswalo district population), or 80 per 100 000 population. This figure is considerably lower than the 1996

national estimate of 361, or the Northern Province estimate of 260. [311] It is higher than the notification rate for the Northern Transvaal (before new provincial boundaries) for 1993 of 53 per 100 000.[309] Until a well functioning district system is established, hospital admission figures will not be an accurate measure of tuberculosis morbidity.

Increases in rates of tuberculosis are to be expected with the advent of the HIV epidemic. A report of admissions to a Hlabisa Hospital, KwaZulu Natal, which serves a population of 150 000, over a 4 year period 1989 to 1992, shows an annual rate of just over 300 until 1992, when it doubled. In 1992, tuberculosis accounted for 7% of all 9000 admissions. This has been attributed mainly to the HIV epidemic in the area.[394] Admissions to a Ugandan hospital for the period 1985-1989 doubled, also attributed to HIV-infection.[398] The 11% HIV-positive rate in this study (of those with known results) may be a slight increase on the 10% similarly calculated for the 1992-1994 period (see section 2, chapter 13, page 130). Since not every patient was tested, little can be said about the prevalence. It does appear that the HIV epidemic had not yet impacted on the study region. One third of the untested group were not in the sexually active age groups. Of those tested for HIV, the preponderance of smear positive disease and of pulmonary disease rather than extrapulmonary indicate that tests were probably not done for diagnostic reasons.

Sex and age:

The male female sex ratio for the 4 year period was 2.2:1. The record review study (section 2, chapter 13) discussed a similar patient sex ratio for the earlier period, and possible causes for the higher frequency of male admissions. Three quarters of all cases occurred in adults 15-59 years of age. This is similar to worldwide age distribution statistics which reported 80% of cases in this age group.[45]

Distance:

Sixty percent of all patients lived more than 10 kilometres from the hospital to which they were told to come for treatment. Some of the issues concerning distances were discussed in chapter 13.

Previous episodes of disease:

Readmission figures may not be correct as they are usually recorded by junior nurses without knowledge about the importance of the issue. The problems and the literature relating to this were discussed in chapter 13. The figures probably provide a minimum estimate of previously treated disease. At 15%, this is high, and gives concern for the probable development of drug resistant disease. There were management problems with the 20 people readmitted during the study period, 5% of all admissions. Sputum smear tests were inadequate, and patient treatment and follow-up was inappropriate given the serious nature of potential MDR disease. One should assume that readmissions for tuberculosis indicates that the first course of treatment was unsuccessful. Careful diagnosis of possible MDR, and close monitoring of treatment adherence in such patients is essential. The health service needs to take a patient-centred approach and consider the miseries of continuing illness, constant hospitalisation, and the physical and social constraints that have led to interruptions. Patients readmitted are at high risk of developing untreatable disease, and of exhibiting the same risk behaviours as caused the readmission.[249, 252, 253]

MDR-tuberculosis:

At least 5% of patients had proven MDR, many at a young age. The previous practice of supplying large quantities of drugs for unsupported use at home may have contributed to the MDR disease in at least some of the cases. The rate is higher than the 3% reported for 1990,[312] and may reflect the increase since that time. If the eight MDR patients with no documented

previous admission to Tintswalo hospital since 1992, had in fact not been treated elsewhere, their resistance would have been primary. The treatment of MDR disease was not taken seriously, evidenced by the inadequate bacteriological monitoring and high interruption rates of these patients. They present an enormous community health problem in potential spread of resistant disease, and are a very high cost to the health service. Consideration needs to be given to hospitalising all resistant cases, and perhaps all re-treatment cases, and all new cases for their intensive phase. As emphasised in the discussion of outcome results for the 1992-1994 period, patient treatment adherence was unsupported and un-monitored in this district over a period of years. The resistance rates measured may well be incomplete, and MDR will surely emerge over the next few years. The suggested period for development is 15 years from poor treatment to emergence, shortened to 10 years in the presence of HIV-related disease.[81]

17.2 Diagnosis

Bacteriological coverage of registered cases of pulmonary disease was 94%, better than 81%, the rate for the earlier period. Both these rates are in line with the recommendation that bacteriological confirmation must occur in over 70% of cases.[86] Sixty six percent of the patients were on treatment on the basis of a positive smear, an improvement on the rate of 53% for the earlier period. Several problems are evident. First, a number of patients had tuberculosis tests which were unnecessary as a routine measure, and costly for the service. It has been shown that there is no place for routine culture tests in a control programme in a developing country.[83] Then there were 57 patients (17% of all) who had no bacteriological proof of disease, and may not have had disease.

17.3 Treatment outcomes and factors and their determinants

This study reports outcomes of all patients, and new smear positives. The importance of analysing smear positive patients lies in the potential for disease spread if these patients are not cured, and in the fact that a control programme can be evaluated by its ability to cure new, previously untreated cases. Thus the outcome of this group is a measure of the success or otherwise of the treatment interventions.[184, 186]

The fact that clinics were sampled, but that individual patients were analysed may have created a design effect. However, this did not exist.

Significant improvements in the treatment outcomes of patients were measured over the 4 year period. The change from a successful rate of 61% in the earlier period (possibly more like 44%) to 73% was a good result. Even better was the change from 63% (probably less) to 79% for patients in the district served by the service. For new smear positive patients the "in-district" change from the best estimate of 70% to 81%, was not far from the goal of 85% cure, although this does assume that those who completed treatment were cured. Issues and constraints in the process will be discussed in chapter 20.

The fact that outcomes for patients living outside the district remained unchanged over the entire period, is evidence that improvements were not possible over large distances, and is proof of the need for a district health system which provides for patients in their own districts.

There was a very low overall cure rate of 10%, and 17% for new smear positive cases. This is because sputum smear examinations were not performed on all patients completing treatment. Not one of the 18 reports quoted in the South African literature review, chapter 9, described cure rates. The definition of cure, recommended by international bodies, was, until recently, unknown and unused in the country. Attention will have to be directed to organising end of treatment microscopy. Issues regarding policy, training and provision of

logistics for such testing from clinics will be discussed in chapter 21.

The combined cured and completed outcome rate for the Tintswalo district for the period 1994-1996 was 73%, and for new smear positive patients, 81%. (The combined cured-completed rates will be referred to as the successful outcome rate.) The strict research conditions ensured that this measurement was as accurate as possible. For those patients who did not have supported treatment (72 or 19% of all), successful outcome is assumed on the basis of regular attendance at a health facility. Even for those patients who were supported, especially if they only attended hospital or clinic less frequently than monthly for assessment and encouragement, assumptions of adherence had to be made based on ticks made by supporters on patients' cards, and patients' assurance that they were taking treatment. The study used an objective urine test to confirm adherence, which test had a reported 100% specificity and 100% sensitivity. The test has been recommended to test adherence in patients taking isoniazid.[399] These results confirm the assumptions about adherence. The isoniazid-detection urine test strips proved to be specific, as all five negatives were identified as not taking drugs. It was useful to confirm the high level of adherence in patients who had lay supporters, and were required to collect their own supplies of tablets to take to supporters. A study in the United States of patients on treatment of active tuberculosis and on preventive treatment showed good agreement between different measures of adherence. These included urine tests at home or at clinics, clinic attendance, number of bottle openings (electronically measured), and remaining pill counts.[400] Routine urine testing in a control programme would be expensive and time consuming, and could detract from efforts to identify non-adherers by other means. If those five patients in this study who were not taking their treatment had had the confidence, resultant upon trusting relationships with health workers, to report their problems, non-adherence could have been avoided. Attention needs to be directed to k-

non-attenders, and to attempting to identify patients at risk of non-adherence.

Interrupted outcomes:

Most patients who interrupted their treatment had moved away from their homes, were untraceable or refused treatment. In view of the lack of job opportunities in this area, it is not surprising that many people had to seek work elsewhere, and probably moved away from their homes as soon as they felt better, before their treatment was complete. Alcohol and substance abuse were said to be problems in those who refused.

The higher proportion of incomplete treatment in patients from outside the district boundaries underlies the purpose of a district health system which seeks to provide accessible health services for defined populations.[367]

Deaths:

The deaths reported in this study include death from any cause that occurred during treatment for tuberculosis. Some deaths may have been missed, as non-returning patients classified as interruptors may have died at home, perhaps in the "not found" category of interrupters. A study of all deaths that occurred during treatment for tuberculosis during the four and a half year period, 1992 to mid 1996, was completed within this research programme. Evidence from patient records, or from live patients (in two cases!) was that 12 cases of the original 80 registered, should not have been counted as deaths. Careful investigation of records, or, in cases where death occurred at home, verbal autopsies done with relatives, showed that death due to tuberculosis was definite, or likely in only 39 of the remaining 68 cases (57%), and possible in a further 21 (31%). However, for 8 of the 68 (12%), tuberculosis was not the cause of death, or unlikely to have been the cause of death.[401]

Transfers:

As discussed in chapter 13, there are problems inherent in the South African context in

maintaining contact with patients who move to other districts and provinces, many of whom have no fixed address in the place to which they move. The treatment outcomes of such patients can not reasonably be the responsibility of the facility that transfers patients elsewhere. However it is important to ensure an adequate transfer process whereby the patient becomes the responsibility of a new health authority. The ideal transfer processes were not observed to occur in this district. The proportion of patients transferred was small (11 of 414 patients or 3%), such that exclusion had little effect on overall and on new smear positive case outcomes. Without the transferred patients, successful outcomes of 75% were achieved for both the total group and the smear positive patients.

Monitoring of treatment with sputum bacteriology:

An inadequate proportion (55%) of patients had microscopy tests two months after treatment. There did not appear to be any selection bias in the testing. Eighty six percent, 156 patients, were negative, a slightly higher rate than the 75% reported by Rieder, who found that positive results at 2 months were predictive of positives after 4 months of treatment.[148] The two month monitoring is recommended as an indicator of response to treatment,[136] so that positives can remain on the intensive phase of drugs for another month.[136, 137]

In our study six of the 25 positive results at 2 months had unsuccessful outcomes - two failed, and 4 interrupted. Bacteriological conversion (cure) was measured for only three of the 19 who were positive at two months (the rest were completers). Numbers were too small to calculate an accurate predictive value of a positive test at two months.

The proportion of tests done at two months was similar at all treatment places, despite the special attempt to implement this policy at intervention clinics. This reflected the inability and some unwillingness of the clinic staff to set up a system for speciment collection and transport to hospital.

Tests after six months were done on only 30% of patients, despite the policy to prove cure at the end of treatment by measuring microscopic conversion to negative. The proportion was marginally higher at intervention clinics (35% compared with 26% at the hospital).

The tests, both at 2 and 5-6 months, were the responsibility of the clinics or the hospital, depending where patients were assigned for their follow-up care. For clinics, the dispatching of specimens to the hospital laboratory was done by the research nurse, who made repeated attempts to establish routines within the clinic functions of taking the specimens, organising transport to the hospital laboratory, using pharmacists, ambulances and other regular visiting district health staff. The results indicate that the system did not work. The problems in implementation will be discussed in chapter 20.

Treatment groups:

When the proposal for decentralised treatment was first discussed in the district, clinic staff were concerned that the clinic workload would increase due to patients being referred for tuberculosis follow-up care. The figures for referrals to the intervention clinics during the study period indicate relatively small numbers, with a range of 12 to 36 patients over the 18 month period. There were not more than seven tuberculosis patients at a clinic at any one time, and slightly more than that fig re at the health centre. The hospital tuberculosis outpatient clinic still carried a heavy b rden of patients for whom the hospital was the closest facility, and who came from o er districts - 273 patients or 68%. With complete decentralisation of patients to their nearest clinics, this rate would, according to the admission figures of this period, be 28% (113 of 403) of the previous load. With the impending increase in patient numbers consequent on the HIV epidemic, decentralisation would be essential if patients are to be managed properly.

The absence of a higher rate of successful outcomes in the treatment clinic group, into which much effort and research resources was channelled, was interesting. The study hypothesis was that intervention at district clinics would facilitate higher rates of treatment completion than would occur within the routine system of hospital-based follow-up. It might have been postulated that the "hospital" group who lived close to their source of care, would be the next best, and that "control clinic" patients who had far to travel, would perform the worst.

There are several possible explanations for the improvements at all treatment places in the district. In addition, there are possible reasons why the clinics did not perform better. The latter will be the subject of chapter 20, where the issues in decentralising care in a rural district will be analysed.

Reasons for general improvements:

i) Contamination of intervention:

There is no doubt that much interest and attention was devoted to tuberculosis by the hospital and community service team. To a small extent this may have reflected early attempts of the "new" South Africa to recognise the enormity of the tuberculosis problem, and to correct past mistakes. However these attempts had not really reached this rural area at the time of this study. The presence of the research team with new ideas, and with resources, facilitated the progression of the initial guarded reaction of the hospital tuberculosis team to an enthusiastic collaborative effort. A research office was created which was shared by the hospital community team, consisting of the nurse and health educators, and the researchers. Workshops run for staff of treatment clinics were attended by the hospital and community team. A spirit of competition was engendered by the study, resulting in determination by the team responsible for hospital-based patients to do better, even though this was not voiced.

ii) **Increased attention to and by patients:**

Every patient in the district, was interviewed 3 times by the researchers. (This aspect of the study will be reported in chapter 18) While no information was given during the course of the interviews, questions were invited at the end of each and answered by an appropriate staff member. The interviews focused the attention of patients on their disease, and provided support and interest in any physical, financial or social constraints to their treatment completion, since questions were specifically directed to these issues.

What is of great importance is that the results at the clinics were as good as those at the hospital, dispelling the fears of some that clinic staff would not cope with the extra load of tuberculosis cases. In fact many became enthusiastic about the new challenges. There were increasing workloads at clinics with increasing numbers of patients, entitled to, and requesting free primary care as part of new national policy. Numbers of cases of tuberculosis will not decrease, despite the better treatment outcomes, as poor management over many years, and the impending disaster of HIV-related tuberculosis will cause more cases, some resistant to drugs.

The overall 75% new smear positive success rate, with 81% for patients living in the district, and the 82% for those attending decentralised intervention clinics, was achieved with great effort. Further improvement must be possible, but will require greater attention to better management at district level, targeted action towards interruptors through recognition of risks and attention to patient-centred care, and bacteriological proof of smear positive conversion. The presence of treatment supporters was shown in the multivariate logistic regression to be associated with successful outcomes. A high proportion of patients in the district had

supporters organised for their community-based treatment. The concentrated effort of the research team resulted in a supporter rate of 98% for intervention clinic patients. Other treatment groups in the district had high rates. Patients who were close to the hospital were paradoxically lowest (81%), as organisation of supporters for this group would appear to be the easiest. Only 47% of those outside the district were supported. Management of patients from outside the district was not really the responsibility of the Tintswalo tuberculosis team, who were already constrained by lack of time and vehicles to monitor their own area. The proper management of these patients depends on an efficient network of services in neighbouring districts, and on good referral systems.

Shopkeepers were the most frequent supporters (39%), reflecting the accessibility of shops throughout the district, and the willingness of patients and shopkeepers to participate in this activity. Wilkinson described the successful involvement of shopkeepers for 33% of his patients, and that half of all supporters were non-health workers.[354] With the large distances between people's homes and clinics, the use of non-health workers was essential. The use of family members has been debated. Although they are accessible and usually caring, objectivity may be lost, and emotional involvement may be constraining. In this study, health workers did not play a large role in patient supported treatment. Community health workers, theoretically appropriate people for this task, were too few and geographically inaccessible. For patients in the district, successful outcomes were associated with high supporter rates however often they attended a clinic or hospital for assessment and collection of drugs. Those from outside managed on their own to achieve success, attending less frequently and with lower rates of support. Patients unable to attend monthly because they lived far away, were in special need of supporters, but this was impossible to organise from another district. Supporters should have a role in encouraging patients to attend services for their regular

appointments, and in reporting problems. Clarification and definition of what they do needs to be discussed with community groups. Training and monitoring, as well as incentives (not necessarily financial) and appropriate communication channels need attention.

DOTS, implemented through treatment support, has received much attention in global tuberculosis control programmes. The history of DOTS demonstrates effectiveness, from the time of Fox's work in 1958,[187] reviews by Sbarbaro and Bayer for the period 1966 to 1977,[189, 190] studies in the United States,[140, 191] Kenya,[193] Nepal[194] and South Africa.[354] This study was not a randomised trial of DOTS, and there may have been some degree of selection biases inherent in the patients for whom support was organised. This did not apply to the intervention clinics, where all patients had support.

Supported treatment is but one part of the total DOTS strategy, and not a cure-all intervention.[207] There needs to be careful consideration of the implications of delegating an important task to untrained lay people, without support or incentives for them.

Distance less than 10 kilometres from the hospital, for all those who attended there, was associated with better outcomes, although this relationship did not feature in the multivariate analysis. Other studies have looked at the influence of distance on adherence. A study in Thailand found that travelling time of more than 30 minutes was associated with lower adherence,[209] another from India, studying tuberculous meningitis in children, found that "local" patients' adherence was better.[292] In Ghana during the 1980s, longer home-to-clinic distances were significantly associated with higher interrupted rates,[294] and accessible services had a positive effect for refugees on the Thai-Cambodian border.[296] A lack of association was described from Cambodia in 171 admissions in 1992.[283] The latter study showed equal proportions of attenders and "absconders" in different distance categories from the treating

hospital, and that non-attenders did not mention distance as a problem. However the study does not explain any link between poverty, as stated by the majority of patients, and distance.

Previous treatment has been described as a risk for interruption of treatment.[286, 299] This study has confirmed those findings, with previous treatment being a highly significant factor in unsuccessful treatment in the multivariate analysis results. Such patients pose special problems as high risks, and warrant consideration of hospitalisation for the duration of their re-treatment.

It is difficult to draw conclusions about treatment outcomes in the arbitrarily defined areas. There did appear to be a higher rate in one area with 11 interrupters (14% of the 77 in that area). Distance from most of this area to the hospital was not an obvious factor as it was within reach of the main taxi route to Tintswalo. There was no intervention clinic here, the only area in the district without one. The population of this area were mostly Sotho speaking. A large part of this area, named Greenvalley, was undergoing rapid urbanisation with a high population density. It is possible that beliefs and customs played a part in the acceptance of medical treatment of tuberculosis. Health workers should acquire some knowledge about local communities.

When patients who attended their local clinic (treatment clinic group) were excluded from the results of treatment outcomes of those who had to travel to the hospital, the results were unchanged, confirming results of similar outcomes in the different treatment groups.

It is of interest that sex and age did not influence adherence. It could have been postulated that

women would be more likely to complete because of their greater permanency in their home districts, and the fact that they are said to use less alcohol, both of which characteristics could promote better treatment adherence. There may be constraints for women, although the presence in their households of young children was not shown to be a factor. Age was not associated with outcomes. Literature from South Africa is conflicting. One study from Soweto shows that age under 30 years is predictive of clinic attendance,[343] others point to under-5-year-olds and teenagers being at risk.[351] Reviews of Sumartojo and Mellins refute the concept of demographic factors having any role in outcomes.[249, 286]

HIV-infection has been shown in the Hlabisa district to be associated with a greater risk of interrupted treatment.[154] It may be that our study does not have large enough numbers to demonstrate this.

Period of admission:

The result that young children were less likely to be admitted could be expected, as primary disease is generally milder, and could be managed on an outpatient basis. Admission periods were long, with nearly 40% of patients staying more than 4 weeks. This partly reflects the severity of illness, patients being very ill on admission. A higher proportion of patients had more than one month admission period than during 1992-1994 (38% compared with 26%). The excess was accounted for by 26 patients on re-treatment regimens, not used before 1994, and resulting in admission periods of up to 8 weeks.

If transfer to a district clinic were possible, where adherence could be monitored, many prolonged admissions might be prevented, and patients' social costs, and health service financial costs reduced. The cost-effectiveness of community-based supported treatment

following a short in-patient period has been proven.[198] However the large distances that patients have to travel to clinics, and the great need to cure tuberculosis may mean that admission for all or part of the intensive phase is essential.

The absence of any influence of **admission, and of a minimum admission period** was surprising, since it would seem logical that even a minimum period would aid the completion rate. During in-patient stays, information and education was given to patients (although these were not evaluated). In addition, there may have been informal discussions between patients that could contribute to their knowledge, and lead to behaviours that would ensure completed treatment. Menzies, reporting on Canadian patients, found that an initial period in hospital was associated with better adherence.[217] There was no information about admissions on a number of patients who had died. This may have introduced bias in the comparisons of outcomes. However, with exclusion of deaths there was no association between outcomes and admission periods.

17.4 Conclusions

Conclusions from this study listed here will be incorporated into the final conclusions of the study in chapter 20, which includes those from the interview studies.

* *Tuberculosis services decentralised to district clinics can and did achieve good results.*
* *Tuberculosis services must plan for an increase in number of cases consequent upon the HIV epidemic, which had not impacted on this area up until 1995.*
* *There is a need for a district system to organise and deliver health services, including those for tuberculosis, to a defined population, geographically accessible to them. Accurate measurement of health problems and populations for rate determinations cannot be achieved without such a health system.*
* *Community supporters are a valuable source of assistance to patients, and contributed to the success of treatment systems. The system needs careful planning for recruitment, training, incentives, and evaluation.*
* *Attention needs to be directed to systems for bacteriological monitoring of patients*
* *Patients who transfer to other services need specific management, and deaths of patients while on treatment need to be accurately documented.*
* *Policies for hospital admissions need to be formulated, taking into account the need to cure patients in order to prevent MDR, and the costs of hospitalisation and resources required. Longer periods of admission were not associated with better outcomes.*
* *Patients previously treated for tuberculosis are high risk, and need special attention.*
* *Deaths are more likely in older male patients. When those who die are excluded, age and sex were unrelated to treatment outcomes.*

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